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HANDBOOK OF DIALYSIS THERAPY

Allen R. Nissenson | Richard N. Fine
Rajnish Mehrotra | Joshua Zaritsky

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HANDBOOK *OF*
DIALYSIS THERAPY

SIXTH EDITION

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This book is dedicated to the heroic patients and care givers who showed courage and perseverance during the COVID-19 pandemic and inspired us all.

Allen R. Nissenson, MD

I would like to dedicate this edition of Handbook of Dialysis to my wife of ALMOST 50 years, Shawney, whose encouragement, support, and advice have made the journey to facilitate access to ESRD care for children of all ages possible, as well as our 4 children, one of whom (Jeffrey) is no longer with us, 11 grandchildren, 2 of whom aspire to become physicians AND 3 GREAT-GRANDCHILDREN. They have tolerated my conflicting priorities over the years. I appreciate their continued understanding.

Richard N. Fine, MD

This book is dedicated to my wife, Kushi Mehrotra, who has stood patiently by my side for 29 years, to our two children, Kunaal and Ria, who have grown into amazing young adults in the blink of an eye, and to my parents, Trijugi and Kamini Mehrotra, who are no longer with us but forever in our hearts.

Rajnish Mehrotra, MD, MS

I would like to dedicate this book to my children, Sarah and Ella.

Joshua J. Zaritsky, MD, PhD

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Preface

The delivery and financing of dialysis care have continued to evolve rapidly throughout the world. The United States has seen the continued consolidation of the dialysis providers, with two large organizations now overseeing the care of two-thirds of all patients. In addition, younger as well as older and sicker patients are now surviving multiple chronic illnesses such as diabetes, hypertension, and congestive heart failure and congenital diseases, and progressing through chronic kidney disease (CKD) to end-stage kidney disease (ESKD), entering dialysis, or seeking conservative care. In addition, in the United States, there has been a major shift in government policy regarding kidney disease with increased emphasis on kidney transplantation, home dialysis, and the care of CKD patients prior to the development of ESKD. These have led to advances in care delivery focusing on patient-centric, holistic care and emphasized the need for care coordination and true integration of care across providers and sites of care. In such an integrated, patient-centric world, an increasing number of providers are taking a financial risk in ensuring quality outcomes. Elsewhere in the world, the rising middle class in countries such as India, China, and throughout the Middle East has seen the concomitant rise of "life-style" illnesses, including obesity, hypertension, and diabetes, and ultimately CKD and ESKD, putting pressure on care providers and governments to deliver and pay for the care of millions of patients. The increasing affluence has also facilitated the extension of CKD and ESKD care to infancy and early childhood.

The objective of the initial edition of *Dialysis Therapy*, published in 1986, was to enlist the involvement of preeminent individuals in areas of clinical dialysis to address, in a succinct fashion, the pertinent clinical problems encountered in adults and children undergoing dialysis. The intent was to provide a "how-to" approach to help the potential reader solve specific patient problems. *Dialysis Therapy* was developed to help nephrologists (pediatric and adult), nurses, technicians, and other members of the health care team resolve the myriad problems confronting the patients undergoing dialysis.

Over 30 years have passed since the first edition of this book was published, but the goals remain the same. To provide those who care for CKD and ESKD patients a simple, readily accessible resource to enable the highest quality care for patients.

The current format has been substantially updated to enable easier access to information and searching for key topics. New chapters and authors have been added, and we have again paid particular attention to the readability of the text, tables, and figures. Resizing of the book to make it more portable and the abundant use of color are additional enhancements.

We wish to thank all of our contributors for their outstanding work and hope that this book will be a useful reference for physicians, nurses, technicians, dieticians, social workers, and administrators, all of whom assiduously attempt to optimize the clinical care of the CKD and ESKD population. The editors wish to thank Nancy Duffy, Meghan Andress, Priyadarshini Pandey, Ryan Cook, and Manchu Mohan, from Elsevier, whose invaluable assistance made the publication of this text possible.

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HANDBOOK *OF*
DIALYSIS THERAPY

PART I

Dialysis Therapy for Adults

SECTION 1

Overview of ESKD

1

Demographics of the End-Stage Renal Disease Patient

JAMES B. WETMORE, MD, MS • KIRSTEN L. JOHANSEN, MD

Introduction

End-stage kidney disease (ESKD) constitutes an ever-increasing threat to public health. Since the publication of the last edition of this book in 2015, complex trends have continued to evolve in the epidemiology of ESKD and maintenance dialysis. In this chapter, we highlight how incidence rates of treated ESKD have increased globally, a phenomenon that will almost certainly continue as low- and middle-income countries undergo economic growth and experience improvements in access to health care, including dialysis. In many developing countries, the challenge posed by the growth of the incident ESKD population will therefore be to overcome the barriers hindering the creation of an adequate dialysis infrastructure. For many high-income countries, the overall growth in the population receiving dialysis has been fueled mainly by an increase in prevalent patients receiving maintenance dialysis, although incidence rates have also continued to increase in many such countries. Prevalent dialysis patients in the United States, for example, are now living substantially longer than they did a decade ago. In developed countries, then, the struggle will be to provide healthcare for ever-aging populations with ESKD and multiple comorbid conditions. In developing and developed countries, policy makers and public health officials face major challenges in confronting the growth of ESKD.

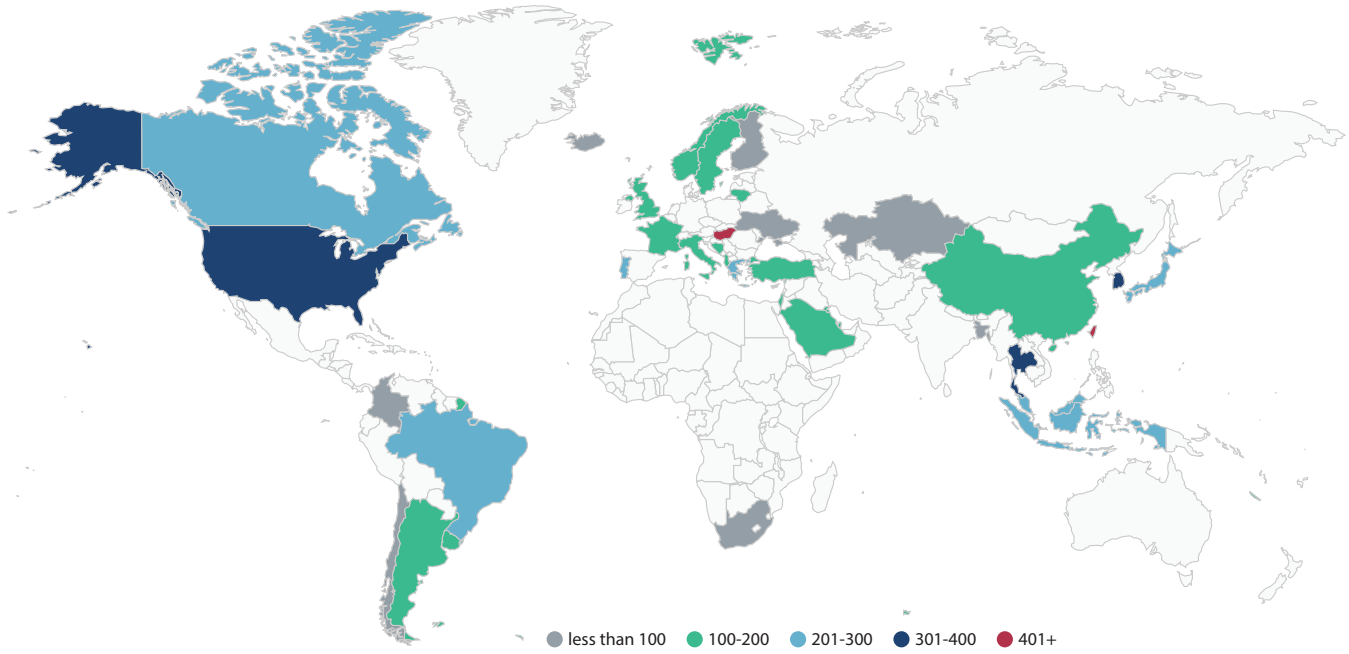
In this chapter, we review demographic data from the United States and other counties to provide background for subsequent chapters. Most U.S. data are derived from the United States Renal Data System (USRDS) (www.usrds.org), which also collects data from some other countries that contribute to this registry.

Incidence and Prevalence of ESKD

International data on treated ESKD incidence and prevalence are published annually in the USRDS Annual Data Report. "Treated" ESKD refers to the provision of life-sustaining maintenance dialysis (typically, in-center hemodialysis, home hemodialysis, peritoneal dialysis) and kidney transplantation. Note that the quality and completeness of international data are likely to vary substantially by country. As such, the data presented should not be viewed as definitive. Nevertheless, they can provide the foundation for inferences about overarching trends.

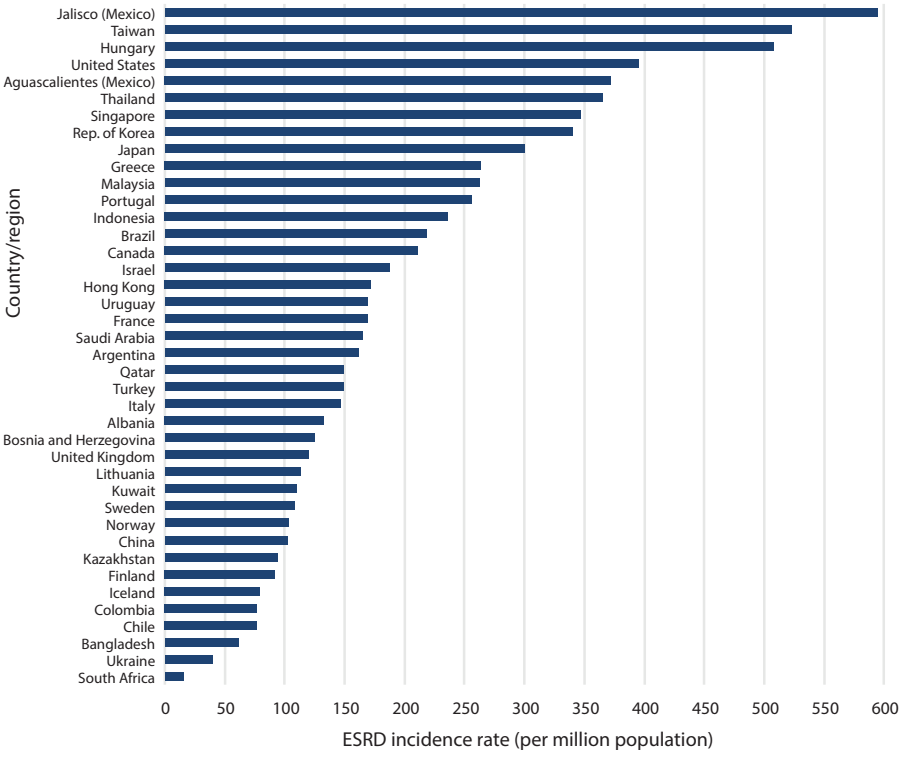
Worldwide, the incidence rate of treated ESKD varies tremendously (Fig. 1.1). Incidence rates reported by participating countries in 2018 are shown per million population (pmp) by country or region in Fig. 1.2. The Jalisco state in Mexico (594 pmp) and Taiwan (523 pmp) have the highest incidence rates, followed by Hungary (508 pmp) and the United States (395 pmp). Several developing countries or areas, many of which have large populations, have extremely high incidence rates, such as the Mexican states of Jalisco and Aguascalientes (372 pmp), Thailand (365 pmp), Malaysia (262 pmp), Indonesia (236), and Brazil (218 pmp).

The 10 countries with the largest growth in incidence rate between 2009–2010 and 2017–2018, plus the United States, are shown in Fig. 1.3. Growth over this period is particularly striking in Asia, which contains 7 of the 10 countries with the largest increases in incidence rates. However, 6 of the 10 countries or regions with the largest growth in incidence rate are classified as lower- or middle-income areas. Among developed countries, which generally provide near-universal access to ESKD treatment (particularly maintenance dialysis), substantial differences exist: the annual growth in treated ESKD incidence rate between 2009 and 2018 remains very high in Hungary (39.9 pmp per annum), South Korea (19.4 pmp per annum), Singapore (12.8 pmp per annum), and Taiwan (11.1 pmp per annum), and somewhat high in Greece (7.6 pmp per annum), Canada (4.4 pmp per annum), the United States (3.3 pmp per annum), and Hong Kong (an affluent part of China, 3.2 pmp per annum). Growth is more modest in Portugal (1.0 pmp per annum) and nonexistent in countries (Israel, Norway, Sweden, Italy, Bosnia and Herzegovina, Colombia, Chile, and Turkey).



2020 United States Renal Data System Annual Data Report. Data source: Special analyses, USRDS ESRD Database. Data presented only for countries from which relevant information was available. All rates are unadjusted. Data for Canada excludes Quebec. Data for Italy representative of 38% of the ESRD patient population. Data for Mexico includes Jalisco and Aguascalientes only. Data for Japan includes dialysis patients only. United Kingdom: England, Wales, Northern Ireland (Scotland data reported separately). Hungary data for incidence count include acute kidney injury. NOTE: Data collection methods vary across countries, suggesting caution in making direct comparisons.

• **Fig. 1.1** Geographic Variation in Incidence of Treated *ESRD*, by Country or Region, 2018.



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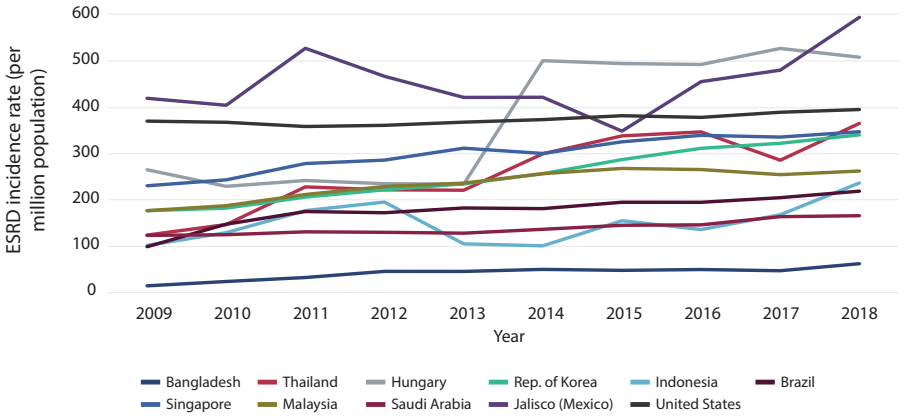
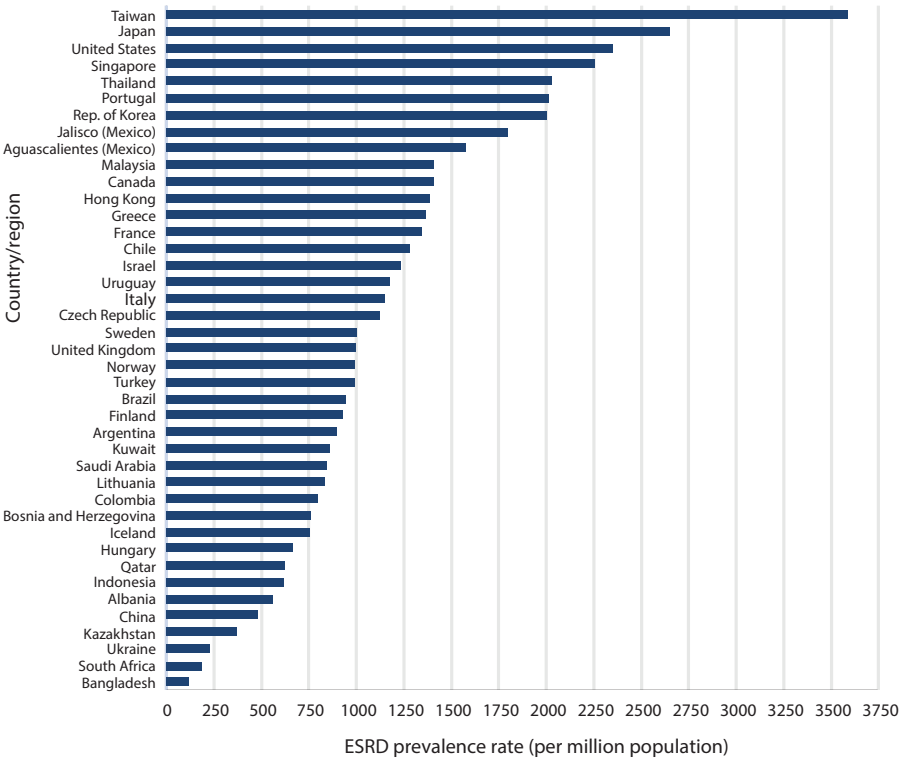
• **Fig. 1.2** Incidence of Treated *ESRD*, by Country or Region, 2018.



2020 United States Renal Data System Annual Data Report. Data source: Special analyses, USRDS ESRD Database. Data presented only for countries from which relevant information was available. All rates are unadjusted. (a) Ten countries having the highest percentage rise in 2017/18 versus 2009/10, plus the U.S. NOTE: Data collection methods vary across countries, suggesting caution in making direct comparisons.

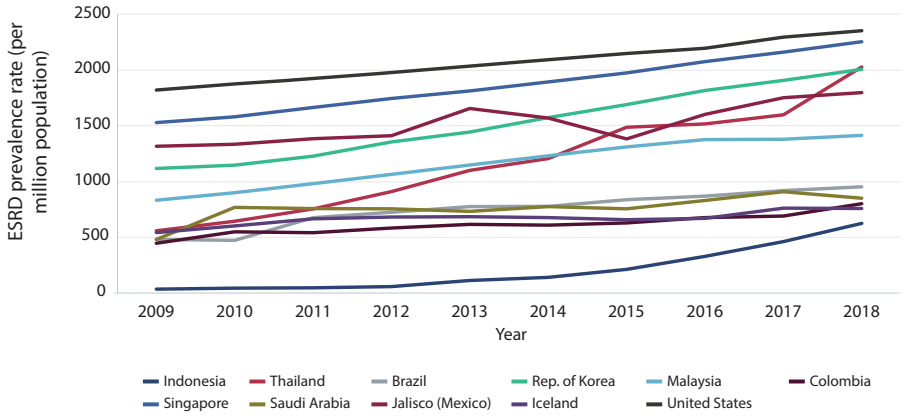
• **Fig. 1.3** Countries or regions with the largest percentage increase in incidence of treated *ESRD*, plus the United States, 2009–2010 versus 2017–2018.



2020 United States Renal Data System Annual Data Report. Data source: Special analyses, USRDS ESRD Database. Data presented only for countries from which relevant information was available. All rates are unadjusted. Data for Canada excludes Quebec. Data for Italy representative of 38% of the ESRD patient population. United Kingdom: England, Wales, Northern Ireland (Scotland data reported separately). NOTE: Data collection methods vary across countries, suggesting caution in making direct comparisons.

• **Fig. 1.4** Prevalence of Treated *ESRD*, by Country or Region, 2018.

The prevalence of treated ESKD, particularly the growth in prevalence rates over the past several decades, is prodigious. Prevalence rates of treated ESKD are shown by country, pmp, in Fig. 1.4. Taiwan (3587 pmp), Japan (2653 pmp), the United States (2354 pmp), Singapore (2255 pmp), Thailand (2028 pmp), Portugal (2014 pmp), and South Korea (2006 pmp) all exceed a rate of 2000 pmp. Average yearly change between 2009 and 2018 is shown in Fig. 1.5, which demonstrates the growth in the worldwide burden of treated ESKD over this period.



2020 United States Renal Data System Annual Data Report. Data source: Special analyses, USRDS ESRD Database. Data presented only for countries from which relevant information was available. All rates are unadjusted. (a) Ten countries having the highest percentage rise in 2017/18 versus 2009/10, plus the U.S. NOTE: Data collection methods vary across countries, suggesting caution in making direct comparisons.

• **Fig. 1.5** Countries or regions with the largest percentage increase in prevalence of treated *ESRD* plus the United States, 2009–2010 versus 2017–2018.

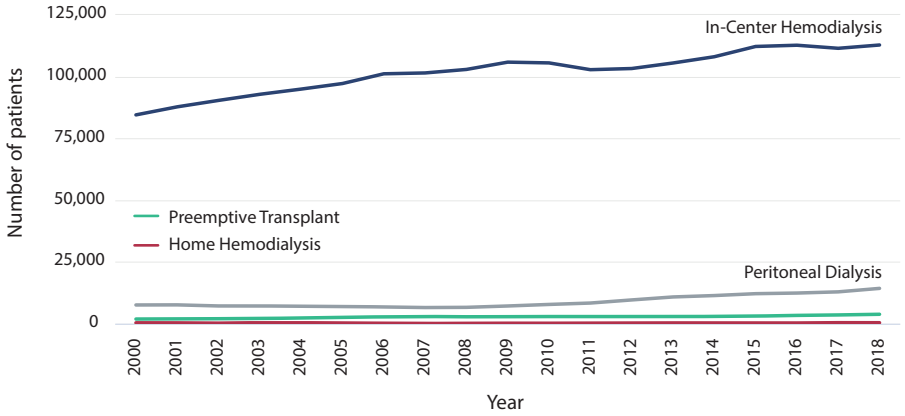
Particularly detailed information on the incidence and prevalence of treated ESKD is available in the United States. Trends in the adjusted incidence of ESKD in the United States are shown in Fig. 1.6. The annual number of incident patients, shown by ESKD treatment modality in Fig. 1.6A, reveals recent growth in the counts to 131,636 in 2018, representing a year-over-year increase of approximately 2% (i.e., relative to 2017)—most of which is due to growth in patients receiving maintenance hemodialysis. *Adjusted* incidence rate (accounting for growth in the U.S. population) was 374.8 pmp in 2018, however, a mere 0.2% increase from 2017 (Fig. 1.6B). This represents a modest decrease from the incidence rates that characterized the first decade of the millennium when rates routinely exceeded 400 pmp.

Year-over-year changes in the prevalence of treated ESKD in the United States are shown in Fig. 1.7. The number of prevalent patients per year (Fig. 1.7A), shown by ESKD treatment modality, demonstrates that the count in 2018 was 785,883, roughly a 3% increase from 2017. Of these, 485,052 (61.7%) were receiving maintenance in-center hemodialysis, 10,350 (1.3%) were receiving home hemodialysis, 58,636 (7.5%) were receiving peritoneal dialysis, and 229,887 (29.3%) were living with a functioning kidney transplant; 1958 (0.2%) were receiving a dialysis modality that could not be determined from administrative claims. The year-over-year percentage growth has generally declined since 2010 when the annual increase was 4%, but the United States has continued to add >20,000 individuals to the prevalent count annually since 2004. The adjusted prevalence rate (Fig. 1.7B) is 2242 pmp, representing a 1.5% increase from the previous year. Annual growth in the prevalence rate has ranged between approximately 1% and 2% since 2007, suggesting that the ESKD (and therefore the dialysis) population will continue to grow for the foreseeable future.

Incidence and prevalence rates are not evenly distributed geographically in the United States (Fig. 1.8). For example, adjusted ESKD incidence rates (Fig. 1.8A) are highest in parts of the Ohio River Valley, southern Texas, southern and central inland California, and parts of the southeast. Adjusted prevalence rates (Fig. 1.8B) reveal a similar, but not identical, pattern. Prevalence also varies by demographic characteristics: adjusted rates of ESKD prevalence are growing fastest in older populations (ages ≥65 years) and among Black Americans (Fig. 1.9A–B). The former finding suggests that older and possibly sicker patients are surviving longer on dialysis than in previous years. The latter finding is not surprising, as Black Americans receiving dialysis tend to survive longer than members of other races (for reasons that remain uncertain).

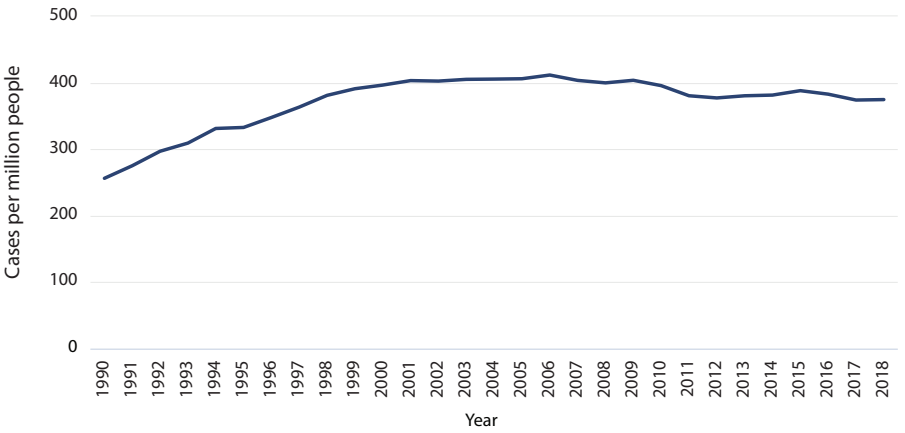
Dialysis Initiation: Predialysis Care and Modality Selection

The transition from predialysis chronic kidney disease (CKD) to ESKD is an area of intense clinical and research interest. In the United States, the percentage of patients with nephrology care in the year before the onset of treated ESKD varies substantially, as shown in Fig. 1.10, which illustrates this finding by Health Service Area. Overall, in 2018 fewer than one-third of patients received nephrology care for more than a year prior to ESKD onset, and only about one-half received this care for more than 6 months, a situation that worsens with unemployment (Fig. 1.11) and other socioeconomic factors. This is extremely disappointing given the near-universal automated laboratory reporting of estimated glomerular filtration rates (eGFR) in the United States. If significant improvements in the care of CKD patients are to occur, overcoming barriers to nephrology care is imperative.



2020 United States Renal Data System Annual Data Report. Data source: USRDS ESRD database.

A



2020 United States Renal Data System Annual Data Report. Data source: USRDS ESRD database.

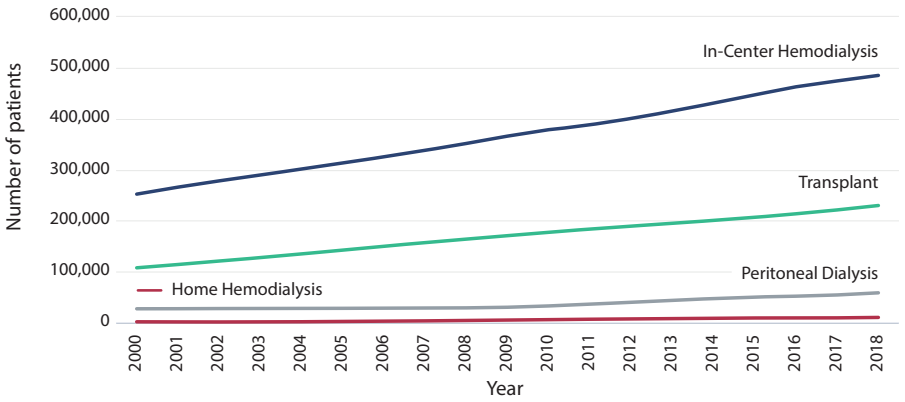
B

• **Fig. 1.6** (A) Number of Incident ESRD Patients, by Modality, 2000–2018. (B) Adjusted Incidence of ESRD, 1990–2018.

While the largest single group of individuals initiating treatment for ESKD is those aged 45–64 (the vast majority of whom initiate in-center hemodialysis), approximately 23% of the incident treated ESKD population is aged ≥75 years, a group that constitutes <7% of the general U.S. population. Likewise, African Americans, who represent approximately 12% of the general U.S. population, make up almost exactly one-quarter of the incident-treated ESKD population (the vast majority of whom also initiate in-center hemodialysis). Diabetes was the cause of incident treated ESKD in approximately 47% of incident patients, and hypertension was the cause in approximately 29%.

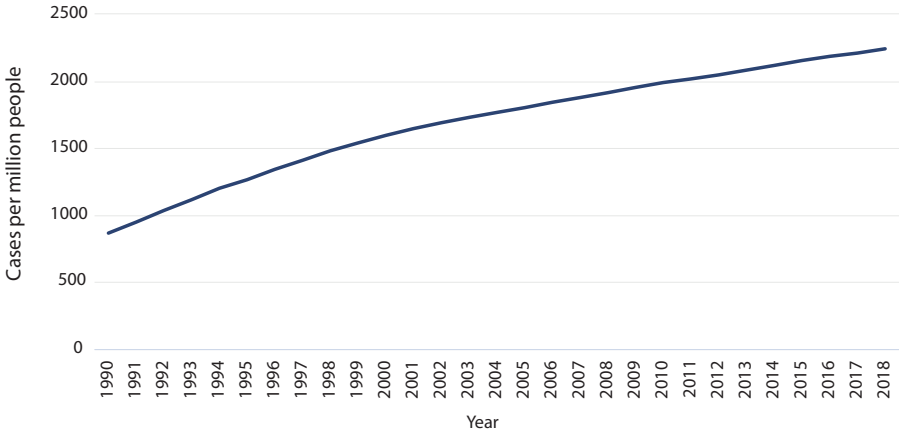
Dialysis initiation at higher eGFR levels had been a growing trend in the United States between 2000 and 2010; this trend began to reverse slightly in the last decade, but was relatively unchanged between 2015 and 2018 (Fig. 1.12). The slight decrease in eGFR levels at which patients are initiating may be the result of a seminal clinical trial addressing this issue. The percentage of patients initiating dialysis with an eGFR of 5–10 mL/min/1.73 m^2 has increased since 2011. However, efforts designed to promote initiation of dialysis at lower levels might allow more time for fistula maturation, a potential benefit given that optimizing vascular access remains a vexing problem. As shown in Fig. 1.13, the use of a catheter at hemodialysis initiation is the norm and, unfortunately, has decreased only slightly over time, from 82.4% in 2009 to 80.8% in 2018. Use of an arteriovenous fistula at hemodialysis initiation increased slightly over this period, from 14.4% to 16.2%. Furthermore, most patients initiating hemodialysis in 2018 (65.2%) did so with a catheter but *without* a maturing arteriovenous fistula or graft. Unfortunately, this represented an increase from 60.2% of patients in 2013. Although this failing is likely related to healthcare system issues and patient-level factors, nephrologists and others involved in the care of patients with advanced CKD must work to improve the rate of hemodialysis initiation with a fully developed arteriovenous access.

Hemodialysis remains, by far, the most common dialytic modality for the treatment of ESKD globally (Fig. 1.14), although in some countries transplantation is used more commonly (as a percentage) than dialysis, including Norway, Finland, Sweden, the UK, several states in Mexico, and Hong Kong. Countries and territories with the largest total proportion of home-based,



2020 United States Renal Data System Annual Data Report. Data source: USRDS ESRD database. ESRD prevalence was identified on December 31 of each year.

A



2020 United States Renal Data System Annual Data Report. Data source: USRDS ESRD database. ESRD prevalence was identified on December 31 of each year.

B

• **Fig. 1.7** (A) Number of Prevalent *ESRD* Patients, by Modality, 2000–2018. (B) Adjusted Prevalence of ESRD, 1990–2018.

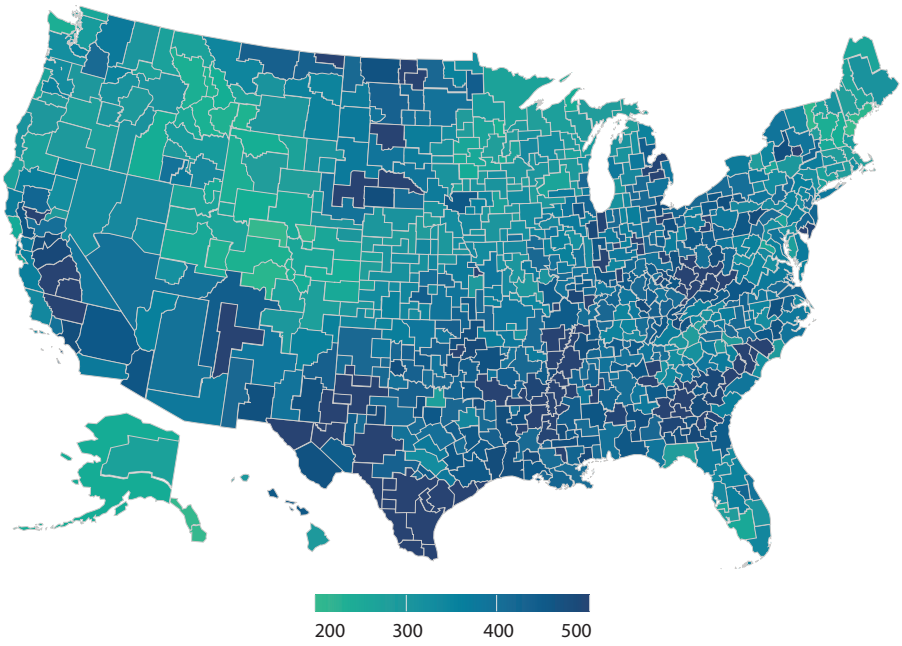
compared to in-center based, therapies (that is, peritoneal dialysis and home hemodialysis) are Hong Kong (the only location where use exceeds 50%), the Mexican states of Jalisco and Aguascalientes, Colombia, and, to a lesser degree, Canada. That some developing countries have successfully implemented relatively high use of peritoneal dialysis is important, since the infrastructure requirements for hemodialysis (the dialysis facility itself and its expensive and complex reverse osmosis system) entail substantial costs. For developing countries, peritoneal dialysis may be the modality most suitable to the challenges of a growing ESKD population.

Home hemodialysis deserves particular comment. In the United States, use of home hemodialysis in prevalent patients grew substantially over the past 10 years; between 2016 and 2018 alone, the prevalent population grew by 16% (Fig. 1.15). Patients receiving home hemodialysis represent a distinct clinical minority; if this therapy is to become more widely utilized, studies examining the factors associated with the adoption and, especially, sustainability of home hemodialysis—and indeed of peritoneal dialysis as well—must be conducted.

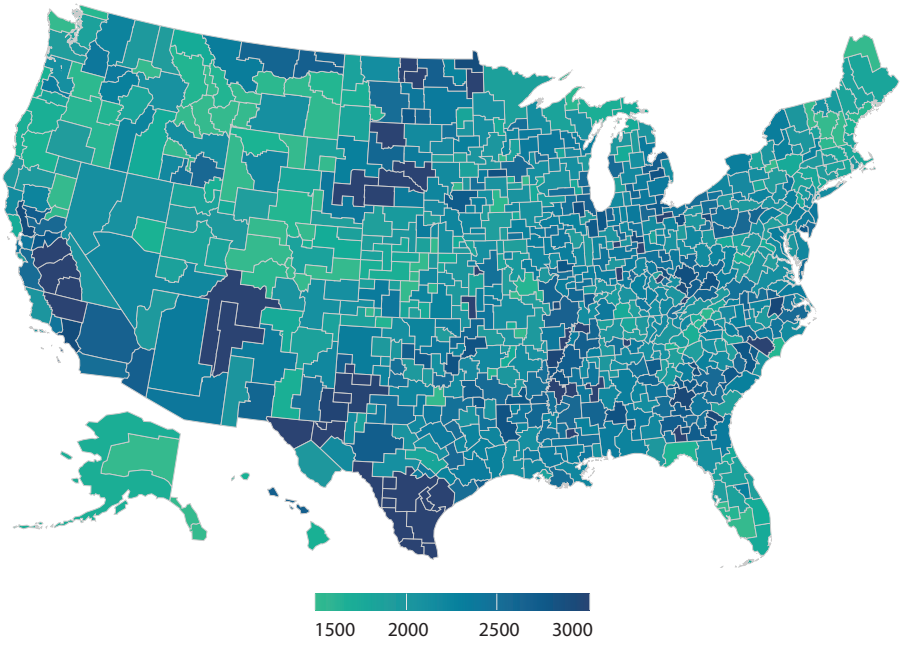
Comorbidity, Expected Survival, and Causes of Death

Mortality rates in patients receiving dialysis in the United States fell substantially between 2009 and 2018. As shown in Fig. 1.16, adjusted mortality rates in patients receiving dialysis decreased from 190 pmp in 2009 to 161 pmp in 2018, a reduction of > 15%. The improvement in mortality among patients receiving peritoneal dialysis was approximately 20%, with the adjusted mortality rate decreasing from 164 pmp to 131 pmp. It is important to note however, that most of the decline in mortality rates occurred during the first half of this period, so future gains are far from assured.

A decade of improvement in the annual mortality rate is particularly impressive given the burden of cardiovascular



A 2020 United States Renal Data System Annual Data Report. Data source: USRDS ESRD database.

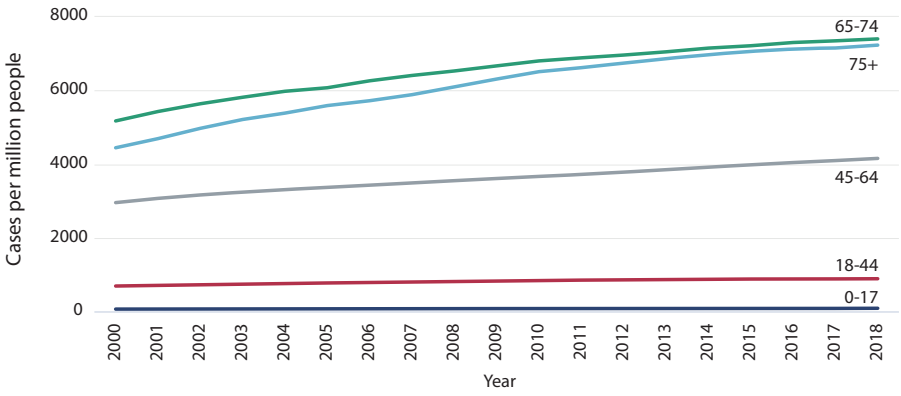


B 2020 United States Renal Data System Annual Data Report. Data source: USRDS ESRD database.

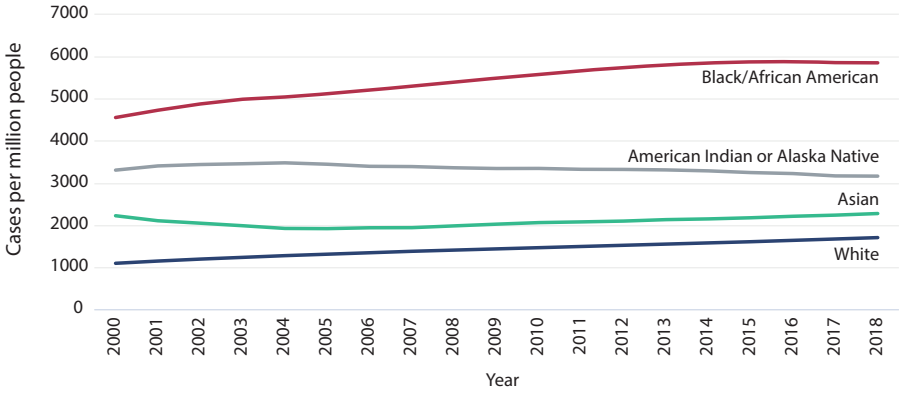
• **Fig. 1.8** (A) ESRD Incidence Rate (Cases per Million People), by Health Service Area, 2017–2018. (B) ESRD Prevalence Rate (Cases per Million People), by Health Service Area, 2017–2018.

disease (CVD) among patients receiving dialysis. Percentages of patients with key CVD diagnoses are shown in Fig. 1.17. The prevalence of CVD was 76.5% in patients receiving hemodialysis and 65.0% in patients receiving peritoneal dialysis. The most common CVD diagnoses were: heart failure (in 44.2% and 31.1% of patients receiving hemodialysis and peritoneal dialysis, respectively), coronary artery disease (43.8% hemodialysis, 36.4% peritoneal dialysis), and peripheral arterial disease (41.5% hemodialysis, 27.7%, peritoneal dialysis).

Despite improvement over time in mortality rates among patients receiving dialysis, the adjusted mortality rate in 2018 in patients receiving dialysis was far higher than for patients with other major medical conditions who were not receiving dialysis. Adjusted mortality rates per thousand patient-years are shown in Fig. 1.18 for U.S. Medicare beneficiaries aged

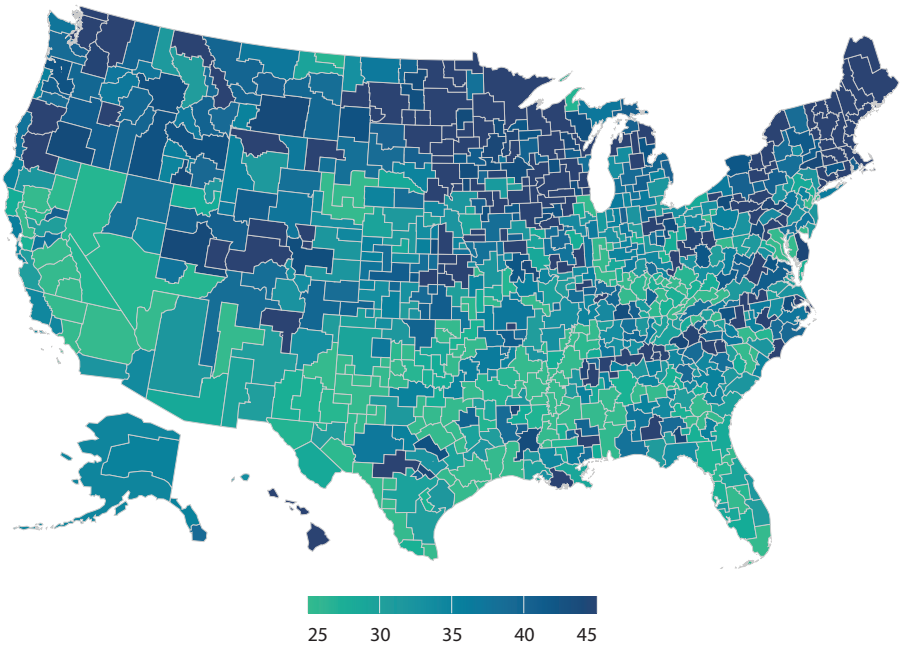


A 2020 United States Renal Data System Annual Data Report. Data source: USRDS ESRD database. ESRD prevalence was identified on December 31 of each year.



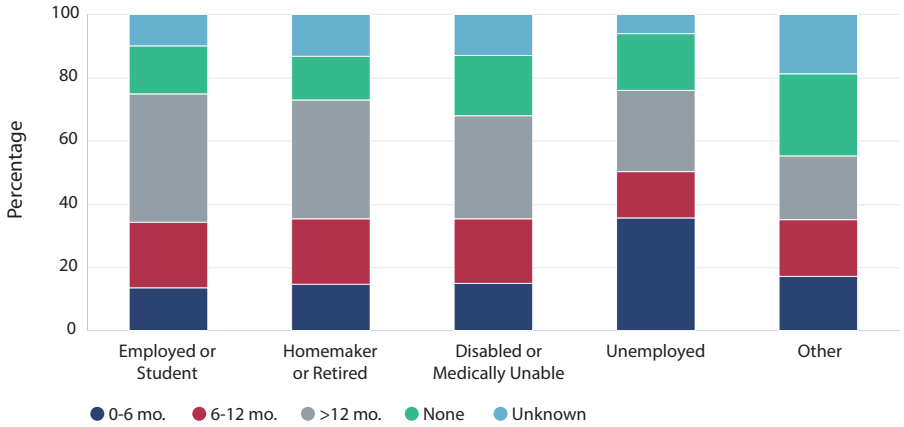
B 2020 United States Renal Data System Annual Data Report. Data source: USRDS ESRD database. ESRD prevalence was identified on December 31 of each year.

• **Fig. 1.9** (A) Adjusted *ESRD* Prevalence Rate, by Age, 2000–2018. (B) Adjusted ESRD Prevalence Rate, by Race, 2000–2018.



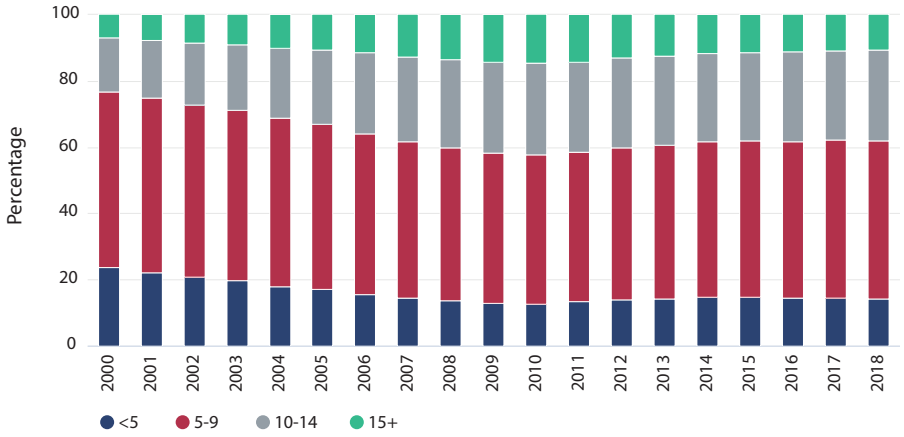
2020 United States Renal Data System Annual Data Report. Data source: USRDS ESRD database and form CMS-2728 (ESRD Medical Evidence Report).

• **Fig. 1.10** Prevalence (%) of > 12 Months of Pre–ESRD Nephrology Care Among Incident ESRD Patients, by Health Service Area, 2017–2018.



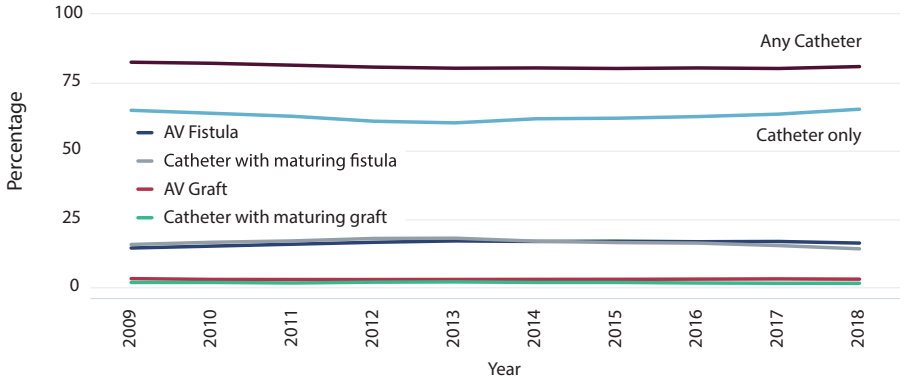
2020 United States Renal Data System Annual Data Report. Data source: USRDS ESRD database and form CMS-2728 (ESRD Medical Evidence Report).

• **Fig. 1.11** Duration of Pre–ESRD Nephrology Care Among Incident ESRD Patients, by Employment Status, 2018.



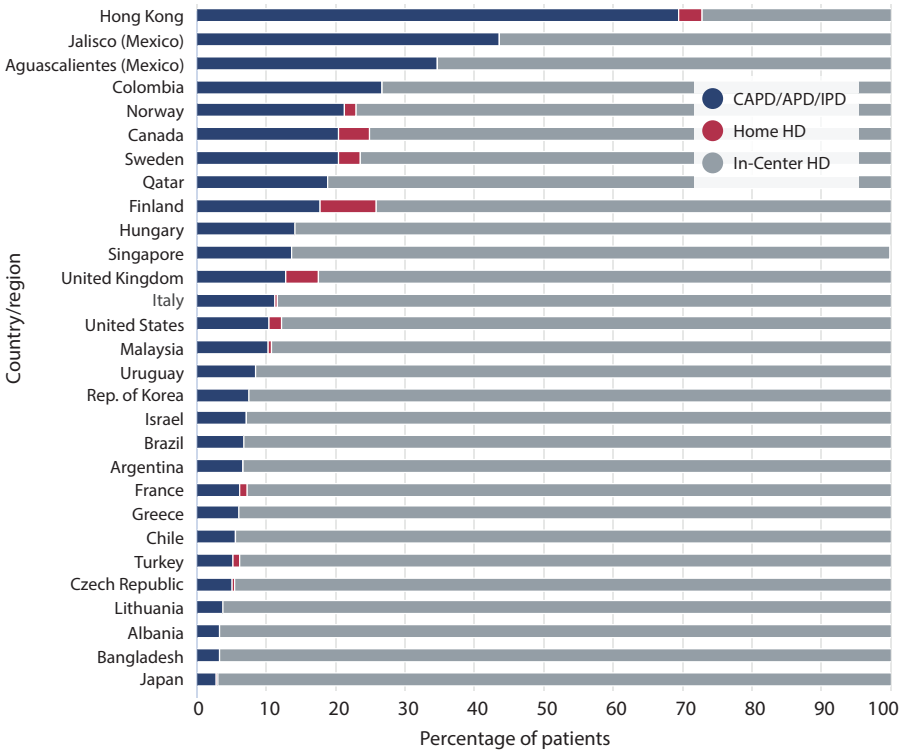
2020 United States Renal Data System Annual Data Report. Data source: USRDS ESRD database and form CMS-2728 (ESRD Medical Evidence Report).

• **Fig. 1.12** Estimated GFR (mL/min/1.73m²) Among Incident ESRD Patients, 2000–2018.



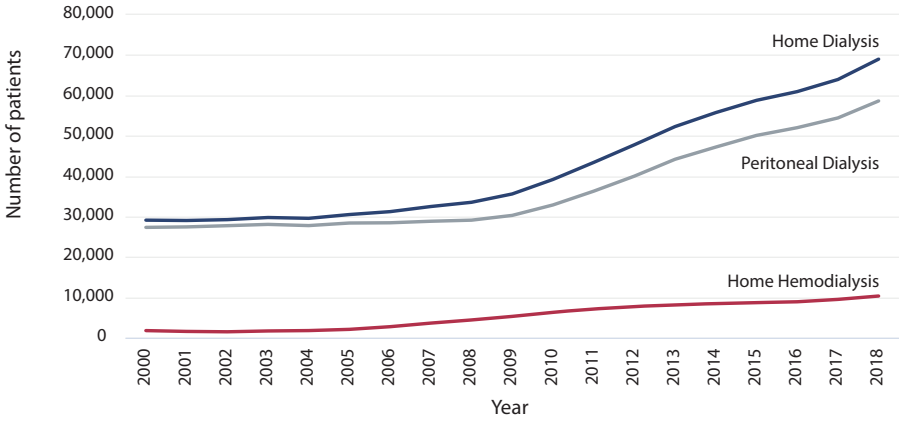
2020 United States Renal Data System Annual Data Report. Data source: ESRD Medical Evidence Report (CMS 2728). Incident patients with ESRD aged 18 years or older initiating hemodialysis between January 1 and December 31 of each year.

• **Fig. 1.13** Vascular Access Use at Hemodialysis Initiation, 2009–2018. *AV*, Arteriovenous.



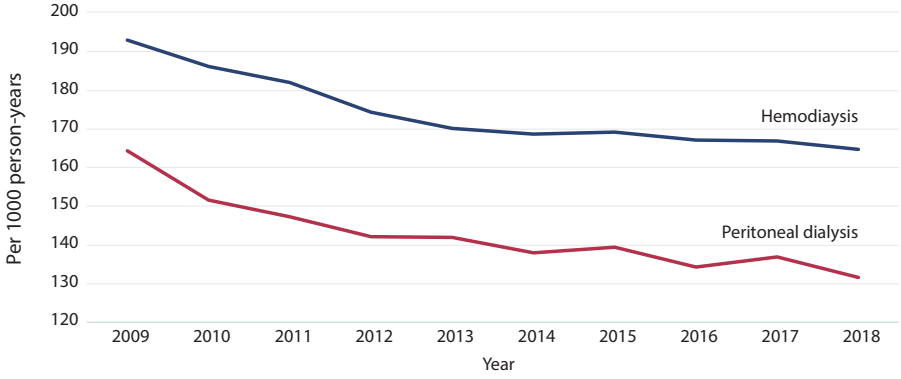
2020 United States Renal Data System Annual Data Report. Data source: Special analyses, USRDS ESRD Database. Data presented only for countries from which relevant information was available. Denominator was calculated as the sum of patients receiving HD, PD, Home HD; does not include patients with other/unknown modality. Data for Canada excludes Quebec. Data for Italy representative of 38% of the ESRD patient population. United Kingdom: England, Wales, Northern Ireland (Scotland data reported separately). NOTE: Data collection methods vary across countries, suggesting caution in making direct comparisons.

• **Fig. 1.14** Distribution of Dialysis Modality in Prevalent Patients with *ESRD*, by Country or Region, 2018.



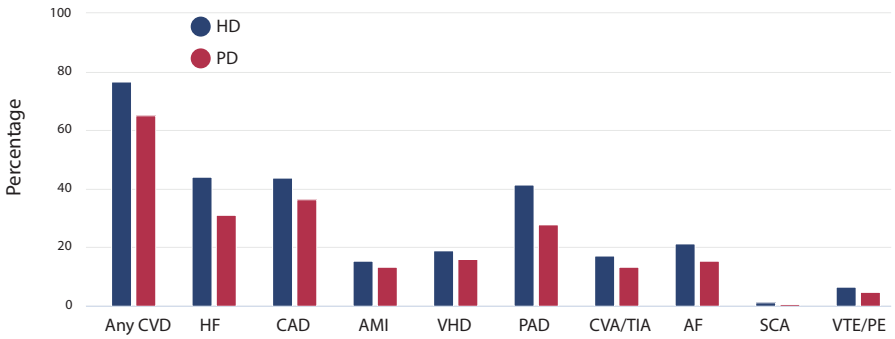
2020 United States Renal Data System Annual Data Report. Data source: USRDS ESRD database. ESRD prevalence was identified on December 31 of each year.

• **Fig. 1.15** Number of Prevalent *ESRD* Patients Performing Home Dialysis, 2000–2018.



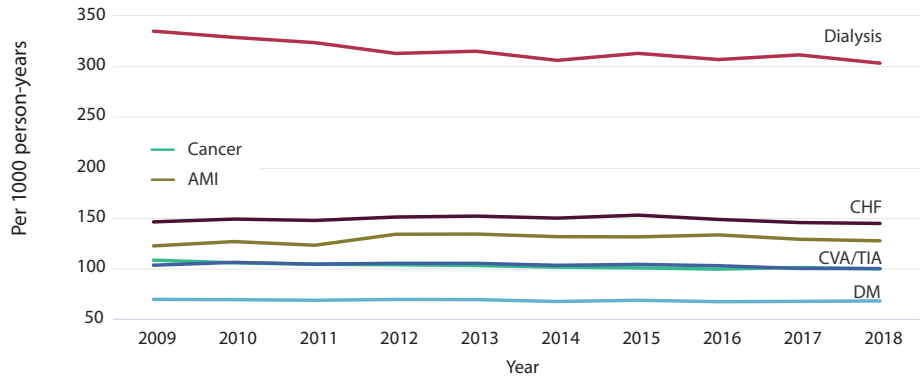
2020 United States Renal Data System Annual Data Report. Data source: ESRD database. Yearly period prevalent ESRD patients 2009-2018. Age, sex, race, ethnicity, and ESRD cause were used in adjusted analyses.

• **Fig. 1.16** Adjusted All-Cause Mortality for Patients With Prevalent *ESRD*, by Treatment Modality, 2009–2018.



2020 United States Renal Data System Annual Data Report. Data source: USRDS ESRD Database. January 1, 2018, point prevalent patients with ESRD aged 18 and older with Medicare Parts A and B coverage. Abbreviations: SCA, sudden cardiac arrest; VHD, valvular heart disease; VTE/PE, venous thromboembolism, and pulmonary embolism.

• **Fig. 1.17** Unadjusted Prevalence of Common Cardiovascular Diseases in Adult Patients with *ESRD*, by Treatment Modality, 2018.



2020 United States Renal Data System Annual Data Report. Data source: ESRD database and Medicare 5% database. 2009-2018 January 1st point prevalent ESRD patients and Medicare fee-for-service beneficiaries without ESRD, all were 66 years or older, at least one year Medicare coverage before January 1st. Age, race, and sex were used for adjustment.

• **Fig. 1.18** Adjusted Mortality Rates Among Patients with ESRD (by Modality) or Comorbidity-Specific Medicare Populations aged ≥66 Years, 2009–2018. *AMI*, acute myocardial infarction; *CHF*, chronic heart failure; *CVA*, cerebrovascular accident; *DM*, diabetes mellitus; *ESRD*, end-stage renal disease; *TIA*, transient ischemic attack.

≥66 years. The mortality rate among patients receiving dialysis was more than twice as high as that of patients with heart failure or a history of acute myocardial infarction and about three times as high as that of patients with a history of cancer or a stroke/transient ischemic attack.

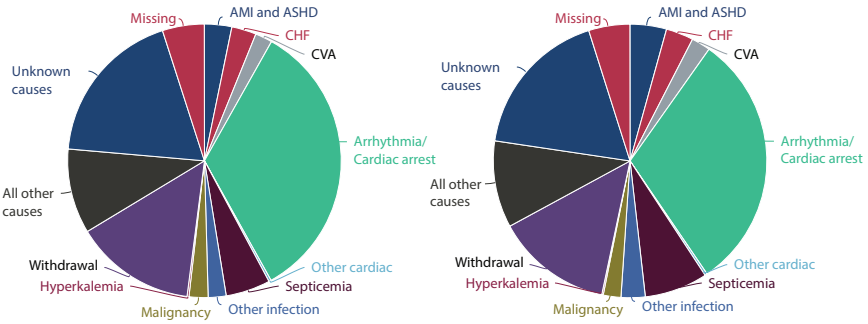
The expected remaining years of life are shown, by age strata, in Table 1.1 for U.S. patients receiving dialysis in 2018 and, for comparison, the general U.S. population, using data derived from the 2017 National Vital Statistics Report. The table illustrates the foreshortened projected lifespans among patients with ESKD relative to those without. For example, among patients aged 40–44 years, there is a >30-year projected lifespan difference between women receiving dialysis (expectancy 10.2 years) and women in the general population (expectancy 40.3 years); the difference is >25 years in men receiving dialysis. Even among patients aged 80–84 years, women and men receiving dialysis live 5.3 and 4.3 years less, respectively, than individuals in the general population.

Causes of death in patients receiving dialysis in the United States are shown in Fig. 1.19 for patients who died in 2018. The most common cause of death, by far, was arrhythmia and cardiac arrest, which is often termed "sudden cardiac death" (SCD). Death was attributed to SCD for 33.8% and 30.7% of patients who died in 2018 receiving hemodialysis and peritoneal dialysis, respectively. Adding the other (non-SCD) causes of CVD-related death increases the percentage who died of a CVD-related cause to 41.9% and 40.8%, respectively. Thus, approximately two in five deaths among patients receiving dialysis are from CVD-related causes. However, more than one in five patients die of an unknown cause or have a missing cause of death, and it is likely that many of these patients also die of CVD-related causes. Withdrawal of dialysis is the attributed cause of death for approximately one in seven patients, but this number may be inflated because dialysis is often electively discontinued in patients whose death from other causes is imminent.

TABLE 1.1 Expected Remaining Years of Life in Prevalent Patients with ESKD and in the General Population, by Age, Sex, and ESKD Treatment Modality

	ESKD Patients, 2018				General U.S. Population, 2017	
	Dialysis		Transplant			
Age	Male	Female	Male	Female	Male	Female
40–44	10.9	10.2	27.9	29.7	36.5	40.3
45–49	9.4	8.9	24.2	25.9	32.0	35.7
50–54	8.0	7.7	20.6	22.2	27.7	31.2
55–59	6.8	6.7	17.2	18.6	23.7	26.8
60–64	5.7	5.8	14.3	15.5	19.9	22.7
65–69	4.8	4.9	11.6	12.6	16.3	18.7
70–74	4.0	4.1	9.5	10.1	12.9	14.9
75–79	3.4	3.6	7.7[a]	8.1[a]	9.9	11.4
80–84	2.9	3.1			7.2	8.4
85+	2.3	2.6			3.7	4.3

ESKD, End-stage kidney disease.
[a]This is for age 75+.
Data source: ESKD database. ESKD 2018 period prevalent patients and National Vital Statistics Report, United States Life Tables, 2017, "Table A. Expectation of life, by age, race, Hispanic origin, race for the non-Hispanic population, and sex: United States, 2017."



2020 United States Renal Data System Annual Data Report. Data source: ESRD database. ESRD patients died in 2018.

• **Fig. 1.19** Unadjusted Percentages of Cause-Specific Mortality, with Inclusion of Missing and Unknown Causes of Death in Patients with ESRD Receiving Dialysis, 2018. *AMI*, acute myocardial infarction; *ASHD*, atherosclerotic heart disease; *CHF*, chronic heart failure; *CVA*, cerebrovascular accident; *ESRD*, end-stage renal disease.

Summary

The number of patients receiving maintenance dialysis continues to grow worldwide. This appears to be attributable primarily to growth in the incident population in developing countries, many of which have likely expanded access to maintenance dialysis and to growth in the prevalent population in developed countries; incidence rates nevertheless remain high in many developed countries. For reasons that are uncertain, patients receiving dialysis in the United States are living longer than they did a decade ago. Governments in all countries, regardless of development status, will have to manage the immense economic and social costs of these growing dialysis populations. Promoting and facilitating "self-care" modalities of dialysis, such as peritoneal dialysis and home hemodialysis, might be the best way to meet these immense future needs. Likewise, governments must improve access to CKD care in an attempt to forestall the anticipated rise in ESKD incidence. Even in a high-income country such as the United States, access to CKD care, including care for the transition from CKD to ESKD, is far from optimal. The trend toward initiating dialysis at ever higher eGFR levels in the United States appears to be abating, a welcome development. CVD remains a major source of morbidity and mortality that must be addressed. These and many other topics will be discussed in subsequent chapters.

Recommended Reading

Brown RS, Patibandla BK, Goldfarb-Rumyantzev AS. The survival benefit of "fistula first, catheter last" in hemodialysis is primarily due to patient factors. *J Am Soc Nephrol.* 2017;28(2):645–652. https://doi.org/10.1681/ASN.2016010019.

Cooper BA, Branley P, Bulfone L, et al. A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med.* 2010;363(7):609–619. https://doi.org/10.1056/NEJMoa1000552.

Liyanage T, Ninomiya T, Jha V, et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet.* 2015;385(9981):1975–1982. https://doi.org/10.1016/S0140-6736(14)61601-9.

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Wetmore JB, Collins AJ. Meeting the world's need for maintenance dialysis. *J Am Soc Nephrol.* 2015;26(11):2601–2603. https://doi.org/10.1681/ASN.2015060660.

2

Uremic Toxicity

RAYMOND VANHOLDER, MD, PhD • GRIET GLORIEUX, PhD

Introduction

The progressive loss of kidney function in chronic kidney disease (CKD) is accompanied by the retention of a host of metabolites due to a decrease in kidney clearance and sometimes in nonkidney clearance that is accompanied by unaltered, if not increased, generation and/or transport. Many of these solutes have been shown to exert biological activity, hence affecting the functioning of cells and organs, resulting in the uremic syndrome. The responsible solutes are then called uremic toxins. The uremic syndrome is a complex amalgam of functional alterations, and many of these impact each other (Fig. 2.1).

The knowledge of the identity and the toxicity of uremic toxins have grown exponentially in the last few years. An encyclopedic listing of known uremic solutes in 2003 identified 90 different compounds, and another 56 were added when this effort was repeated in 2012.

The recent acquisitions of metabolomic and proteomic research are further extending this list. In spite of this almost unlimited possibility for identification, it is more difficult and labor intensive to prove the toxicity of those molecules. Hence, only a limited number of retention solutes have been studied extensively enough to allow a sufficiently underpinned discussion of their toxicity, and this review will be restricted to the most important ones.

To distinguish among uremic toxins, generally, the classification into three major groups as proposed by the European Uremic Toxin Work Group (EUTox) and based on their removal pattern by dialysis is applied. It distinguishes among (1) small water-soluble compounds, (2) protein-bound compounds, and (3) the so-called middle molecules, which are mostly small peptides (Table 2.1). Such subdivision is in part artificial as, in fact, there is a continuum in the molecular weight and the degree of protein binding of uremic solutes.

The content of this chapter is based on a review published by the authors in 2018, classifying the most relevant uremic toxins along with the clinical and experimental evidence of their toxicity (Table 2.2). In that publication, a scoring system was used to identify the solutes with the most convincing evidence of their toxicity. Here, we will discuss one by one the solutes classified in 2018 as most relevant (see Table 2.2—solutes marked in italic), first by summarizing the evidence known at that time, with direct reference to the most pertinent supporting publications, followed by significant data published since the appearance of our 2018 review and informed by an up-to-date search via PubMed using as keywords the name of the toxin on one hand and kidney on the other. Some toxins (e.g., advanced glycation end-products [AGEs]) were considered as a group if, in the literature, they were regularly discussed together. Whether the applied concentrations corresponded to those in uremia was not taken into account, as this implies a systematic review process. This chapter was limited to organic solutes and will thus not deal with inorganic molecules (water, sodium, potassium, phosphorus).

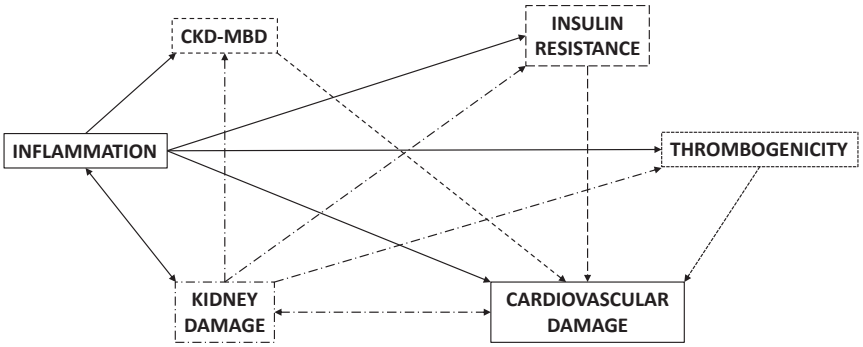
Small Water-Soluble Compounds

The upper molecular weight limit for small water-soluble compounds has arbitrarily been defined as 500 Dalton (Da) (see Table 2.1), and according to their definition, protein binding should be minimal. Complete lack of protein binding cannot be excluded but, in general, should be negligible to have no influence on their removal by dialysis, which is efficient with any type of dialysis, although in some cases hampered by kinetic characteristics.

Asymmetric Dimethylarginine

Asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA) are two guanidines with specific biological characteristics.

Since 1992, ADMA has been identified as a uremic retention compound with potential hemodynamic impact because it inhibits nitric oxide synthase (NOS), hence decreasing the endothelial protective effect of nitric oxide (NO). Of note, ADMA concentration is increased in a host of settings, many of which are linked to CKD (such as diabetes mellitus, obesity, and cardiovascular [CV] disease). ADMA concentration has been linked to CV events and mortality in the general population, as well as in CKD. In healthy volunteers, it was shown that infusing ADMA up to concentrations relevant for uremia had definite hemodynamic effects.



• **Fig. 2.1** Most Important Interfering Systemic Elements of the Uremic Syndrome. *CKD-MBD*, Chronic kidney disease–mineral and bone disorder.

TABLE 2.1 Different Classes of Uremic Toxins as Used in This Publication

Class of Molecules	MW Range	Prototypes	MW Prototype (Da)
Small water-soluble compounds	<500 Da	Urea	60
		Creatinine	113
Protein-bound compounds	Mostly <500 Da	Indoxyl sulfate	213
		p-Cresyl sulfate	188
Middle molecules	≥500 Da	β_2-Microglobulin	11,818
		Retinol binding protein	23,010

Da, Dalton; *MW*, molecular weight.

TABLE 2.2 List of Toxins Considered in Vanholder et al. per Class

Small Water-Soluble Compounds	Protein-Bound Compounds	Middle Molecules
Guanidino compounds	***AGEs***	Adrenomedullin
- Guanidinosuccinic acid	**AOPPs**	Adiponectin
- Methylguanidine	CMPF	Angiogenin
- Guanidine	**Cresols**	Atrial natriuretic peptide
- Creatine	- *P-cresyl sulfate*	β_2-Microglobulin
- Guanidino acetic acid	- P-cresyl glucuronide	β-Endorphin
- γ-Guanidino butyric acid	**Hippurates**	β-Lipotropin
- *ADMA*	- Hippuric acid	Cholecystokinin
- *SDMA*	- P-hydroxy hippuric acid	Complement factor D
Oxalate	- O-hydroxy hippuric acid	Complement factor Ba
Phenylacetylglutamate	Homocysteine	Cystatin C
Methylamines	**Indoles**	*Interleukin-1*β
- (Mono)methylamine	- *Indoxyl sulfate*	*Interleukin-18*
- Dimethylamine	- Indoxyl glucuronide	*Interleukin-6*
- Trimethylamine	- *Kynurenine*	*Tumor necrosis factor-*α
- *Trimethylamine-N-oxide*	- *Kynurenic acid*	*Interleukin-8*

TABLE 2.2 List of Toxins Considered in Vanholder et al. per Class—cont'd

Small Water-Soluble Compounds	Protein-Bound Compounds	Middle Molecules
Sulfuric compounds	**Phenols**	Interleukin-10
- Lanthionine	- Phenyl sulfate	*Endothelin*
Myoinositol	- *Phenyl acetic acid*	*FGF-23*
2PY	Quinolinic acid	*Ghrelin*
Polyamines		Glomerulopressin
- Acrolein		***Immunoglobulin light chains***
- Putrescine		***Lipids and lipoproteins***
- Spermine		Leptin
- Spermidine		MCSF
Urea		Methionine-enkephalin
Carbamylated compounds		*Neuropeptide Y*
Cyanate		Orexin A
Ammonia		*Parathyroid hormone*
Uric acid		Pentraxin-3
Xanthine		Peptide YY
Hypoxanthine		Prolactin
		Resistin
		Retinol binding protein
		Visfatin

Bold characters are used for groups of compounds. Toxins discussed in this publication are given in italic.
Kynurenine and kynurenic acid discussed together as kynurenines.
ADMA, Asymmetric dimethylarginine; *AGEs*, advanced glycation end products; *AOPPs*, advanced oxidation protein products; *CMPF*, carboxy methyl propyl furanpropionic acid; *FGF-23*, fibroblast growth factor 23; *MCSF*, macrophage colony stimulating factor; *SDMA*, symmetric dimethylarginine; *2PY*: *N*-methyl-2-pyridone-carboxamide.
Vanholder R, Pletinck A, Schepers E, Glorieux G. Biochemical and clinical impact of organic uremic retention solutes: a comprehensive update. *Toxins* 2018;10(1):33.

The rise in concentration of ADMA in CKD can, to a large extent, be attributed to a decreased activity of the enzyme dimethylarginine dimethylaminohydrolase (DDAH), which is responsible for the breakdown of ADMA, rather than to a direct decrease of urinary excretion.

Next to its endothelial impact mentioned earlier, the biologic effects of ADMA have mainly been linked to inflammation, cognitive dysfunction, erythropoietin resistance, and procoagulant effects.

In a more recent experimental study, increasing expression of DDAH in the kidney had a positive effect on diabetic nephropathy.

Symmetric Dimethylarginine

SDMA is an isomer of ADMA that, for a long time, has been considered biologically inert. However, a number of studies subsequently showed that SDMA was also biologically active, essentially via decreasing NO production and proinflammatory effects. Via posttranslational modification of high-density lipoprotein (HDL), SDMA has in addition been shown to generate an abnormal lipoprotein inducing endothelial damage.

On the clinical level, SDMA was more significantly correlated to serum inflammatory markers than ADMA, and it also correlated to mortality and CV events in a post hoc analysis of the Hemodialysis (HEMO) study.

In spite of the structural analogies with ADMA, SDMA is not dependent on DDAH for its clearance from the body as it is largely removed by kidney excretion, with a highly significant correlation to estimated glomerular filtration rate (eGFR).

In a more recent study, Hesse et al. demonstrated that the presence of SDMA in dysfunctional HDL was a mediator to cause glycocalyx breakdown. SDMA was a stronger predictor than ADMA of kidney and CV outcomes both in nondialysis CKD and in elderly White individuals.

Trimethylamine *N*-Oxide

Trimethylamine *N*-oxide (TMAO) was also known as a component of uremic biological fluids before a boost in studies on this solute occurred from 2011 onward when Wang et al. suggested a substantial link to CV disease. Intriguingly, in spite of the substantial amount of data supporting the toxicity of TMAO, the compound is also known as a stabilizer of protein structures. Equally paradoxical, fish, as a well-known source of high quantities of TMAO, is protective against CV disease.

The role of TMAO in the spectrum of uremic toxicity has extensively been described in a seminal review published in 2016 by Velasquez et al. TMAO, a small amine oxide, is generated from choline, betaine, and carnitine via intestinal bacterial metabolism after ingestion of certain food products like red meat, shellfish, or cheese. In humans, a positive correlation has been observed between plasma levels of TMAO and CV events and mortality. A number of changes linked to atherogenicity, such as alteration of cholesterol and proinflammatory pathways and foam cell formation, have been described. TMAO plasma levels increase progressively with a decline in kidney function and are associated with mortality in White patients with end-stage kidney disease (ESKD) and the need for CV surgery in CKD.

In more recent studies, in vitro, ex vivo, and in vivo studies demonstrated a role of TMAO in inducing vascular calcification and vascular damage by activation of proinflammatory signals and the inflammasome. The relation of TMAO levels and negative CV and kidney outcomes was confirmed in patients with type 1 diabetes mellitus, but no association with outcomes was found in hemodialysis (HD) patients with moderate to severe secondary hyperparathyroidism. In children with early-stage CKD, TMAO levels were associated with abnormal ambulatory blood pressure measurements and vascular stiffness. Finally, inhibition of TMAO production decreased the formation of atherosclerotic lesions in mice fed a high-choline diet and reduced kidney tubule-interstitial fibrosis and functional impairment in a murine model of CKD.

Carbamylated Compounds

Urea, a marker of uremic retention in CKD and adequacy of intradialytic solute removal, has traditionally been considered to be biologically inert. However, a number of recent experimental studies suggest that urea is toxic at concentrations like those observed in CKD patients. At least five studies indicated that urea itself directly induces molecular changes related to insulin resistance, free radical production, apoptosis, and disruption of the protective intestinal barrier. However, in addition, urea also generates cyanate, and via cyanate carbamylated compounds, which all have been linked to biological changes.

The role of carbamylation in CKD has been extensively reviewed elsewhere. Carbamylation is responsible for post-translational protein modifications resulting in a similar biochemical process as when AGEs are generated (see later). Carbamylated compounds are involved in atherogenesis and other functional changes, such as activation of mesangial cells into a profibrogenic prototype, with the potential to play a role in the progression of kidney failure and modification of leukocyte response to collagens. Carbamylated low-density lipoprotein (LDL) dose dependently induced endothelial cell death and smooth muscle cell proliferation and an increase in monocyte adhesion to endothelium, as well as vascular cell changes of relevance to atherogenesis. In addition, HDL is carbamylated in CKD and inhibits endothelial repair function.

In at least three observational clinical studies focusing on independent HD populations, carbamylated compounds were associated with CV events and overall and CV mortality.

In a more recent study on human vascular smooth muscle cells, protein carbamylation, especially of mitochondrial proteins, exacerbated calcification by suppressing enzymatic inhibition of ectopic calcification. In patients with type 2 diabetes mellitus with eGFR >60 mL/min/1.73 m^2, the risk of deterioration of kidney function was higher in those with the highest concentration of carbamylated LDL and HDL. Carbamylated LDL was no longer associated with kidney outcome after adjustment for baseline eGFR, but the association with carbamylated HDL remained significant. In a crossover randomized controlled trial (RCT), Di Iorio et al. demonstrated that a urea-lowering diet could decrease protein carbamylation in CKD patients, directly underscoring the deleterious impact of nutrition with urea sources on carbamylation.

Uric Acid

Uric acid has been associated with calcitriol metabolism and inhibition of expression on monocytes of CD14, a lipopolysaccharide receptor, and has also been linked to proinflammatory processes, insulin resistance, and nephropathy. All those mechanisms may contribute to hypertension, uremic vascular disease, progression of CKD, and thus mortality.

In a longitudinal clinical analysis, uric acid was associated with CKD progression and vascular stiffness. In the National Health and Nutrition Survey (NHANES) study, it was related to CV complications and overall CV mortality. In a systematic review and meta-analysis of CKD patients, uric acid levels were significantly associated with mortality, even after adjustment for kidney function. Uric acid has also been associated with an increased incidence of acute ischemic stroke and mild cognitive dysfunction. However, in an observational analysis of HD patients from Taiwan, an inverse relation was found between uric acid concentration and mortality. Similarly, in a large HD patient database, low and not high uric acid was associated with mortality, especially in those patients with low protein intake.

Uric acid is one of the only uremic retention compounds whose concentration can be decreased selectively by specific drugs, such as allopurinol, febuxostat, or probenecid. In an

observational study in CKD patients, treatment with allopurinol was associated with improved arterial stiffness and lower overall mortality.

A few RCTs assessing the impact of uric acid–lowering drugs on parameters of endothelial function showed no positive effect, but in at least one other study, allopurinol improved peripheral vasodilator capacity. Allopurinol was shown to decrease blood pressure in young adolescents with newly diagnosed essential hypertension, but in an RCT in overweight adults, uric acid lowering could not lower blood pressure, while a systematic review could also not confirm an impact on blood pressure. In another RCT, in CKD, the group treated with allopurinol had a lower number of CV events and a slower progression of kidney failure, which was confirmed post hoc in a long-term analysis, although, again, a meta-analysis could not support a long-term effect on kidney dysfunction. Finally, an umbrella review including more than 100 studies and 136 outcome parameters, including CKD incidence and progression and mortality in CKD, showed no clear association of uric acid with these parameters.

Thus, in spite of certain arguments for the toxicity of uric acid, essentially based on experimental and observational clinical studies, not all data are consistent, especially in RCTs and meta-analyses considering uric acid-decreasing drugs. This picture may, however, be blurred by the fact that the main pharmaceutical interventions that are effective in decreasing uric acid, allopurinol, and febuxostat, have by themselves a sizeable complication profile.

More recent data confirm these considerations. Publications on pathophysiology point to the role of uric acid in causing inflammation, in injuring the kidneys by reprogramming kidney, immune cell metabolism, and activating the kidney inflammasome. The large majority of publications are, however, observational studies pointing to an association between uric acid concentration and the development or progression of CKD in the general population or in specific groups such as CKD patients with dyslipidemia, early-stage CKD patients, obese adolescents with type 2 diabetes, type 2 diabetics at large, type 1 diabetics, or individuals suffering from dyslipidemia. In addition, the study by Kanbay et al. in the general population also found an association with hypertension, and the one by Pilemann-Lyberg et al. in type 1 diabetics with CKD linked uric acid also to CV events and overall mortality. One meta-analysis found a significant relation between uric acid and a composite endpoint of worsening of kidney function, ESKD, or death, but the study contained only 12 small RCTs representing 832 patients. A recent review pointed to a protective effect on kidney function of uric acid lowering in trials with a decline of GFR in the control group, but not in studies where such a decline was absent.

Summary

Small water-soluble uremic retention solutes can no longer be considered irrelevant to the uremic syndrome, although the role of only a few representatives of this group of compounds in the uremic syndrome is supported by enough evidence to be reported in this chapter (Table 2.3). This is essentially the case for the carbamylated compounds, ADMA, SDMA, and TMAO. In spite of an extensive number of experimental and clinical studies on uric acid, there is continuing debate on its role, mainly related to contradictory results of RCTs and meta-analyses. All four compounds and the group of carbamylated solutes were linked to CV damage, inflammation, and kidney damage. ADMA and uric acid affected the largest number of systems (Table 2.3).

Protein-Bound Compounds

The protein-bound uremic toxins are a heterogeneous group of generally small solutes, which, due to their protein

TABLE 2.3 Physiologic Mechanisms and Organ Systems Affected by the Small Water-Soluble Uremic Compounds

	ADMA	SDMA	TMAO	Carbamylated Compounds	Uric Acid
Cardiovascular damage	X	X	X	X	X
Inflammation	X	X	X	X	X
Neurotoxicity	X				X
Hematology	X				
Thrombogenicity	X				
Insulin resistance					X
CKD-MBD					
Kidney damage (fibrosis)	X	X	X	X	X

ADMA, Asymmetric dimethylarginine; *CKD-MBD*, chronic kidney disease–mineral and bone disorder; *SDMA*, symmetric dimethylarginine; *TMAO*, trimethylamine-*N*-oxide.

binding, are difficult to remove by dialysis. Their protein binding coefficient is, in general, low, although the binding of some compounds may be more stable, especially those generated by posttranslational modifications, such as the AGEs. Many precursors of the protein-bound solutes are generated by bacterial metabolism in the intestine.

For the time being, few therapeutic options exist that specifically can decrease the concentration of this group of solutes, and one of these, the orally administered intestinal sorbent AST-120 (Kremezin^{R}), did not impact the progression of CKD in RCTs.

Advanced Glycation End Products

The role of AGEs in CKD has been reviewed extensively elsewhere. AGEs are generated by the reaction of specific amino acids within the protein structure with the carbamyl group of reducing sugars, which is then stabilized by oxidation. AGE compounds and their precursors are numerous and contain *N*-carboxymethyllysine, pentosidine, hydroxyimidazolone, 3-deoxyglucosone, malondialdehyde, pyrraline, glyoxal, and methylglyoxal. AGE accumulation has first been identified in diabetes mellitus. Because CKD as a condition is also characterized by inflammation, oxidation, and retention, AGE accumulation is a typical feature of CKD, irrespective of diabetic status.

AGEs bind to a number of receptors, among which the AGE-specific receptor (RAGE) plays a central role in several deleterious biological effects. RAGE expression is increased in many inflammatory conditions and also in CKD.

AGEs have a negative impact on body functions and overall outcomes via several mechanisms, among which are induction of oxidative stress, inflammation, and endothelial dysfunction, including quenching of NO. AGEs have also been linked to thrombogenicity, kidney fibrosis, structural bone damage, and neurotoxicity.

With all these functional alterations, it is no surprise that on a more global organic level, AGEs are linked to vascular stiffness, damage, and calcification.

Studies on the links between AGEs and mortality have shown conflicting results, with some studies even showing better outcomes with higher AGE levels. Such results may reflect confounding factors, such as better nutritional status resulting in both higher AGEs and higher survival, or the index AGE may have been a compound with low biological impact or lower vital tissue concentration. In contrast, low serum soluble RAGEs, which are actors protecting against AGE activity, have consistently been associated with CV risk factors and events.

In more recent studies, methylglyoxal-derived AGE induced matrix metalloprotein expression via RAGE and mitogen-activated protein (MAP) kinase signals contributed to kidney cell dysfunction. In a clinical observational study in kidney transplant patients, AGE concentrations were associated with CV mortality. Administering AGE-breaking drugs to rats with CKD decreased vascular calcification, the CKD-MBD marker fibroblast growth factor-23 (FGF-23) (see later), and AGE content in bone, the latter, however, without changes in bone mechanics. Finally, RAGE was shown to be a key element in the generation of vascular calcification.

p-Cresyl Sulfate

Until 2005, it was thought that the intestinal precursor of p-cresyl sulfate, p-cresol, was the representative cresol during uremic retention. However, later on, this view was shown to be the result of an artifact. Shortly after de Loor et al. and Martinez et al. identified the artifact and had stated that in reality the conjugates p-cresyl sulfate and p-cresyl glucuronide were present, an in vitro study by Schepers et al. for the first time pointed to a role of p-cresyl sulfate in causing oxidative stress by activating leukocytes. Soon after this observation, further exploration started on the biological effect of p-cresyl sulfate. This resulted in extensive data on its toxicity, summarized in a systematic and narrative review article.

The role of p-cresyl sulfate in inflammation and other phenomena linked to CV damage, such as cardiomyocyte apoptosis resulting in diastolic dysfunction, was repeatedly demonstrated. In addition, toxic effects on kidney tubular cells, related to tubular cell damage and kidney fibrosis, have also been reported. Finally, p-cresyl sulfate was also shown to play a role in insulin resistance, changes in adipose tissue metabolism, and fat redistribution through the body.

Hence, p-cresyl sulfate contributes in many ways to the mechanisms responsible for CV damage. In line with these pathophysiologic and experimental findings, p-cresyl sulfate has repeatedly been associated with CV complications and mortality in CKD patients in observational studies as well as in a meta-analysis. Total p-cresyl sulfate has also been linked to uremic pruritus.

More recent studies mainly focused on conditions or interventions with a potential impact on p-cresyl sulfate concentrations. In patients with acute kidney injury (AKI), the rise of plasma p-cresyl sulfate did not match that of creatinine, and for a similar serum creatinine, p-cresyl sulfate was lower in AKI than in CKD. A very-low-protein diet and Mediterranean diet in CKD caused a favorable change in gut microbiota and a reduction of plasma p-cresyl sulfate. A meta-analysis underscored the potential of an increase in fiber intake to cause a decrease in p-cresyl sulfate. Finally, Gryp et al. found no arguments in favor of an increase of intestinal p-cresyl sulfate generation as CKD progressed. The progressive increase in p-cresyl sulfate in CKD seemed largely attributable to the loss of kidney function, while data of fractional clearance suggested that tubular clearance was more affected than glomerular clearance. P-cresyl sulfate also decreased glutathione in porcine tubular cells, rendering them more vulnerable to oxidative stress, especially in combination with other toxic sulfates like indoxyl sulfate and phenyl sulfate.

In a post hoc analysis of the HEMO trial, Shafi et al. failed to confirm the association between p-cresyl sulfate

and CV outcomes in dialysis patients. Analytical issues, questioning the accuracy of the free p-cresyl sulfate concentrations and case mix with a majority of Afro-Americans, may explain the discrepant findings with previous outcome studies. Also, in another study by van Gelder et al., levels of p-cresyl sulfate did not associate with mortality and CV events in HD patients enrolled in the Dutch CONvective TRAnsport STudy (CONTRAST). However, total p-cresyl sulfate levels were assessed, in contrast to the previous studies observing an association with free p-cresyl sulfate levels.

Indoxyl Sulfate

Indoxyl sulfate has, in the context of uremic toxicity, definitely been the most extensively studied compound of all tryptophan metabolites and even probably of all protein-bound toxins. Although there has been debate whether the correct concentrations were used in those studies, a systematic review found a substantial number of studies applying the right conditions that showed a toxic effect.

The toxicity of indoxyl sulfate has been extensively reviewed. Substantial experimental evidence of toxicity of indoxyl sulfate points to tubular cell and kidney damage. As retention of indoxyl sulfate increases in rats with failing kidneys, indoxyl sulfate is accumulated in proximal tubular cells. Oral administration of indoxyl sulfate or its precursors caused kidney injury and glomerular sclerosis, while in proximal tubule cell cultures, it provoked inflammation and fibrosis.

Indoxyl sulfate may also damage vessels through various mechanisms. Indoxyl sulfate impairs proliferation and repair of human umbilical endothelial cells, induces vascular smooth muscle cell proliferation, a thrombogenic effect through aryl hydrocarbon receptor (AhR) activation, and the subsequent functional stabilization of tissue factors. Activation of the AhR and tissue factor expression were correlated to each other.

With regard to a potential link to bone disease, indoxyl sulfate has been shown to reduce the expression of parathyroid hormone (PTH) receptors in mouse osteoblasts. In parathyroidectomized rats, animals fed the indoxyl sulfate precursor indole developed reduced bone turnover in tibial bone biopsies.

Clinical evidence of toxicity in humans, however, is only observational, and several studies showed no association. Sporadic data suggest an association between indoxyl sulfate concentration and progression of kidney disease, but controlled studies with the oral sorbent AST-120 administered to decrease plasma indoxyl sulfate could not demonstrate a benefit on kidney function.

In patients with known coronary artery disease and moderate CKD, patients with higher indoxyl sulfate levels had more left ventricular dysfunction. In patients with coronary disease and CKD up to stage 3, higher total serum indoxyl sulfate was related to more hospitalizations because of heart failure and a higher cardiac mortality. Indoxyl sulfate has also been related to more severe coronary artery calcification and cardiac stent restenosis.

Finally, indoxyl sulfate levels were associated with impairment of associative function in CKD stage 3 but not in more advanced stages. A metabolome analysis in HD patients searching for factors related to cognitive dysfunction could not find an association for indoxyl sulfate.

More recent studies essentially focused on various cellular dysfunctions related to uremic symptoms and complications. One study described a pro-oxidative effect and inhibition of NO in endothelial cells by indoxyl sulfate that was counteracted by uric acid. Further studies showed a role for indoxyl sulfate in inhibiting neovascularization, enhancing coagulation, and induction of apoptosis related to oxidative stress in human astrocytes, a mechanism potentially related to neurotoxicity. In addition, indoxyl sulfate increased endothelial permeability via activation of AhR. This effect was neutralized by the antioxidant polyphenol resveratrol. It also induced tumor necrosis factor-alpha (TNF-α) generation via the AhR. Promotion of vascular calcification by medium conditioned by endothelial cells exposed to inorganic phosphate and indoxyl sulfate was suggested to be mediated by interleukin (IL)-8. Indoxyl sulfate was shown to disrupt the blood–brain barrier via AhR activation. Finally, the duration and intensity of indoxyl sulfate exposure were shown to affect osteoclastogenesis via AhR. Indoxyl sulfate also decreased glutathione in porcine tubular cells, rendering them more vulnerable to oxidative stress, especially in combination with other sulfates like p-cresyl sulfate and phenyl sulfate.

Similar to p-cresyl sulfate, Shafi et al., in a post hoc analysis of the HEMO trial, also failed to confirm an association between indoxyl sulfate and CV outcomes in dialysis patients, but the same technical questions on analytical approach and case mix raised previously for p-cresyl sulfate apply here as well.

Indole Acetic Acid

Indole acetic acid, in general, received less attention in uremia research than indoxyl sulfate, but this trend has changed during the last few years. Indole acetic acid has been linked to CV disease by the induction of proinflammatory mechanisms and procoagulant tissue factor production. Similar to indoxyl sulfate, these effects, to a large extent, are linked to the activation of the AhR that seems to play a central role in the biological action of several indoles.

Indole acetic acid also induces proximal tubular injury after uptake via organic acid transporters, stimulates cellular free radical production affecting cell viability, and accelerates the progression of CKD in experimental animal studies. Furthermore, indole acetic acid has been linked to a number of metabolic effects, such as the inhibition of uptake of digoxin and kidney glucuronidation.

In an observational clinical study, indole acetic acid was associated with increased mortality and CV events.

More recent studies confirmed the role of indole acetic acid in tissue factor upregulation, which in human endothelial cells appeared to involve the AhR-mitogen-activated

protein (MAP) kinase-nuclear factor (NF)-κB pathways. Indole acetic acid was also associated with a decrease of stem cell factor expression in a cross-sectional study in maintenance HD patients. Stem cell factor is essential for hematopoiesis and spermatogenesis. In HD patients, indole acetic acid concentration was associated with poor cognitive function. In kidney transplant patients, however, indole acetic acid was not associated with CV risk, in contrast to what was observed in nontransplanted CKD patients.

Kynurenines

Elements of the kynurenic pathway are retained in CKD, because of not only decreased kidney clearance but also metabolic alterations. They increase leukocyte adhesion to vascular endothelium, activate AhR, and decrease lipopolysaccharide-induced production of TNF-α. Injections of kynurenic acid in rats with normal kidney function impaired their cognitive flexibility. Furthermore, they also modify metabolic functions by impairment of hepatic drug uptake, the activity of kidney glucuronyltransferases, and energy metabolism by the rat cerebral cortex.

In the general population, kynurenine levels were associated with all-cause, cancer, and CV mortality, and in patients with stable angina, with myocardial infarction. In patients with ESKD, the kynurenines were associated with oxidative stress, inflammation and prevalence of CV disease, and parameters of hypercoagulability.

More recent reports showed lower kynurenine levels with inhibition of the renin–angiotensin system, but with an inverse correlation to eGFR, while kynurenine/tryptophan ratios were higher in responders to angiotensin receptor blocking, showing a substantial decrease in albuminuria. Blood levels of kynurenine were suggested as biomarkers of chronic heart failure, but again, these values were related to eGFR, as well as to age and C-reactive protein (CRP). Higher urinary kynurenine was associated with nonrecovery from AKI. The kynurenine/tryptophan ratio was also positively correlated with advanced atherosclerosis and the occurrence of major CV events.

Phenyl Acetic Acid

Phenyl acetic acid has been linked to inhibition of inducible NOS expression, osteoblast proliferation and differentiation, enhancement of the formation of oxygen free radicals in vascular smooth muscle cells, and increases of the inflammatory response by polymorphonuclear leukocytes. On the metabolic level, it inhibits kidney cellular solute transport pumps and conjugation by glucuronidation. Finally, in a clinical study, phenyl acetic acid was related to cognitive dysfunction in dialysis patients.

Summary

Similar to small water-soluble molecules, protein-bound solutes have the capacity to affect a host of biological systems that contribute to the uremic syndrome (Table 2.4). This is especially the case for the AGEs and kynurenines as a group and p-cresyl sulfate, indoxyl sulfate and indole acetic acid as individual compounds.

The experimental data supporting the toxicity of protein-bound compounds seem to be more robust than the clinical ones. Indeed, toxins like indoxyl sulfate are not entirely covered by unequivocal clinical data, whereas others like indole acetic acid and phenyl acetic acid have barely been studied clinically in spite of fairly convincing experimental data. All solutes discussed in this section were linked to CV damage and inflammation and almost all to neurotoxicity, thrombogenicity, metabolic changes, and kidney damage. Indole acetic acid impacted the largest number of systems (see Table 2.4).

Middle Molecules

The group of middle molecules is mainly composed of small proteins or peptides that, under normal conditions, can cross the glomerular filtration barrier (< 58,000 Da). Their minimum molecular weight has arbitrarily been set at 500 Da, although most middle molecules have a molecular weight of more than 10,000 Da. In contrast to the small water-soluble compounds and the protein-bound solutes, which, to a large extent, are intestinal bacterial metabolites of nutrition components, most of the middle molecules are generated endogenously. They are often part of homeostatic mechanisms to correct for other uremic changes (e.g., PTH) or are expressed in response to other toxins or triggers (e.g., the cytokines), whereby their concentration depends not only on retention but also on endocrine and paracrine mechanisms. A typical example is PTH, whose concentration changes, to a large extent, are defined by alterations in serum phosphate and bone homeostasis.

Because of their high molecular weight, dialytic removal is possible only with membranes with a large enough pore size (high flux membranes). To the best of our knowledge, few strategies exist to decrease concentrations of specific middle molecules.

β_2-Microglobulin

The interest in β_2-microglobulin, the water-soluble extrinsic light chain of major histocompatibility class I (MHC I) molecules, increased when it appeared to be a major constituent of bone and joint amyloid deposits in patients with CKD, especially those on long-term dialysis. Higher patient age and the use of small pore complement activating cellulosic dialysis membranes compared to large-pore biocompatible AN69 membranes increased the prevalence of the disorder. Once the problem had been recognized, its frequency tended to decrease, which was likely attributable to the large-scale introduction of high flux, noncellulosic dialyzers, and the improvement in quality of dialysis water.

TABLE 2.4 Physiologic Mechanisms and Organ Systems Affected by the Protein-Bound Uremic Toxins

	AGEs	p-Cresyl Sulfate	Indoxyl Sulfate	Indole Acetic Acid	Kynurenines	Phenyl Acetic Acid
Cardiovascular damage	X	X	X	X	X	X
Inflammation	X	X	X	X	X	X
Neurotoxicity	X		X	X	X	X
Hematology				X		
Thrombogenicity	X		X	X	X	
Metabolic changes		X		X	X	X
Insulin resistance		X				
CKD-MBD	X		X			X
Kidney damage (fibrosis)	X	X	X	X		
Itching		x				
Carcinogenicity				X		

AGEs, Advanced glycation end products; *CKD-MBD*, chronic kidney disease–mineral and bone disorder.

A specific role in amyloid generation is attributed to the glycosylation of β_2-microglobulin by, e.g., imidazolone and N^{ε}-carboxymethyllysine. Glycosylated β_2-microglobulin, in contrast to the naive molecule, has a proinflammatory impact on human monocytes with the potential to lead to bone and joint destruction.

In various observational studies, both in nondialyzed and dialyzed CKD patients and populations not specifically selected because of CKD, β_2-microglobulin has been associated with hard outcomes or surrogate outcomes like parameters of inflammation, vascular stiffness, or bone remodeling. Although in some of these studies, adjustments were made for GFR, it is difficult to support the causative role of β_2-microglobulin unequivocally from these data as the concentration of the molecule may sometimes have functioned as a surrogate for (residual) kidney function.

From these observations, the question arises whether, apart from its role in kidney disease-related amyloidosis, β_2-microglobulin should be considered as a toxin by itself or just simply as a marker. A number of studies point in the direction of a biological (toxic) effect. In a proteomic study searching for a biomarker of peripheral artery disease, plasma β_2-microglobulin was a significant discriminator. Kidney function was, however, lower in the affected patients, so that also this study was not unequivocally in support of a pathophysiologic role of β_2-microglobulin. In vivo and in vitro experimental studies showed an impact on osteoclast formation, upregulation of TNF-α and IL-6 generation, and a neurotoxic effect. In a milestone study assessing functional neurologic changes during aging in rodents, β_2-microglobulin was identified as a pro-aging factor, impairing hippocampal cognitive and regenerative function. However, in a study assessing the immunologic impact of β_2-microglobulin by using a commercially available β_2-microglobulin batch, the originally found strong proinflammatory effect disappeared after purification of the β_2-microglobulin solution by in vitro dialysis, suggesting a contaminant in the commercially available product. Hence, any finding of a biological effect of β_2-microglobulin and, by extension, of any uremic toxin should be regarded with caution.

In more recent studies, β_2-microglobulin was independently associated with a more rapid decline of kidney function. Some suggest that β_2-microglobulin is one of the compounds involved in uremic pruritus, although the specific study leading to that conclusion may have been confounded as increased β_2-microglobulin concentration in skin was found in animals with CKD, without indication of causation.

Overall, the clinical suggestion of a link between β_2-microglobulin and negative outcomes is strong but may be confounded by (residual) kidney function and selection bias. Also, in view of the limited biochemical experimental support for a negative action of the compound, available data regarding the toxicity of β_2-microglobulin do not seem completely convincing.

Cytokines

An extensive review has summarized studies on the uremic toxicity of IL-1β, IL-6, and TNF-α with data up to the level of RCTs and IL-8 with data up to the experimental and clinical observational level.

Interleukin-1β

IL-1β has a complex regulation and is released only by macrophages. It was the first interleukin described and is an extremely strong proinflammatory cytokine known to cause disease in humans. Several therapeutic interventions target IL-1β in inflammatory diseases like rheumatoid arthritis, and one of these is the IL-1β receptor antagonist anakinra. Anakinra given for 4 weeks to HD patients with inflammation decreased both CRP and IL-6, in contrast to what was observed in the placebo-treated control group. However, these are only surrogate outcomes. Data on whether anakinra also improves key clinical outcomes are currently unknown.

In more recent studies, IL-1β was shown to induce a metabolic shift in kidney stroma cells, causing tubulointerstitial fibrosis in vitro and murine experimental models. Neutralization of the IL-1 receptor signal attenuated this profibrotic effect. In another study, the role of elevated IL-1β in medial vascular smooth muscle cells by inducing cell senescence and accompanying calcification was suggested, thus contributing to osteoblastic transition of vascular smooth muscle cells. Neutralization of the biological effects of IL-1β in uninephrectomized mice with type 2 diabetes and obesity-related hyperfiltration attenuated the decrease in GFR and preserved the glomerular podocyte number. IL-1β was shown to enhance the generation of FGF-23. In an observational clinical study in nondiabetic HD patients, IL-1β concentration was positively associated with insulin resistance. Most importantly, an RCT assessing the impact of the IL-1β antagonist canakinumab in high-risk atherosclerosis patients with CKD showed a decrease in major CV events in the intervention group, especially in those with the most robust anti-inflammatory response. These novel data corroborate the suggestion of an involvement of IL-1β in the progression of kidney and CV damage.

Interleukin-6

IL-6 is a strong proinflammatory agent mainly secreted by macrophages. The molecular signaling pathways induced by IL-6 have been summarized in the review on cytokines mentioned earlier. In brief, IL-6 elicits proinflammatory activity in conjunction with soluble IL-6 receptor by connecting with membrane-bound glycoprotein (gp)-130, while soluble gp-130 acts as a decoy receptor. Both IL-6 and soluble IL-6 receptors are independent predictors of mortality in ESKD patients. IL-6 has a number of effects that are potentially deleterious to CKD patients. It is a central component of inflammation, acute reactant response, and cachexia. Infusion of IL-6 in humans increased resting energy expenditure, plasma-free fatty acids, and fat oxidation.

More recent data in mice propose a role for IL-6 in anemia of CKD and the production of FGF-23, and in clinical human studies, an association with vascular stiffness in ESKD and coronary artery calcification in CKD was suggested. IL-6 gene polymorphisms and IL-6 concentration are associated with atherosclerosis in CKD patients.

Because of the clinical impact of IL-6, a number of drugs neutralizing IL-6 action have been developed or are under development, but to the best of our knowledge, there are as yet no clinical studies showing a benefit for neutralization of the effects of IL-6 in CKD apart from a number of recent reports on the impact in kidney transplant recipients, especially in patients with COVID-19 pneumonia. However, in mice with unilateral ureteral occlusion, blocking IL-6 trans-signaling by recombinant Fc-gp130 protected against the development of kidney fibrosis. Likewise, the IL-6 inhibitor tocilizumab attenuated in rats with streptozotocin-induced diabetic nephropathy histopathologic changes in the kidneys but without impact on creatinine clearance.

Thus, although there are several data that suggest a pathophysiologic role of IL-6 in uremia, conclusive evidence of its impact still is lacking.

Interleukin-8

IL-8 was the first chemoattractant cytokine to be recognized, and it recruits neutrophils to sites of infection or tissue injury. IL-8 is also tumorigenic and angiogenic. In this way, IL-8 may contribute to the propensity for CKD patients to develop inflammation and tumors. In HD patients, higher IL-8 levels were associated with all-cause and CV mortality.

More recent data point to the promotion of vascular calcification by medium conditioned by endothelial cells exposed to inorganic phosphate and indoxyl sulfate via IL-8.

Tumor Necrosis Factor-Alpha

TNF-α is an important inflammatory cytokine produced essentially in activated macrophages and T cells, but also in other cells, especially when they are stressed. TNF-α induces the release of other inflammatory cytokines, upregulates the expression of endothelial adhesion molecules, promotes cell death, and decreases Klotho expression, an anti-inflammatory and antiaging factor. Infusion of TNF-α decreases free fatty acids, increases glucose appearance, and promotes vascular calcification in non-CKD settings. In CKD, levels of TNF-α are related to malnutrition and inflammation markers, predict mortality, and play a role in the pathogenesis of certain types of kidney damage. In patients with rheumatoid arthritis and CKD, treatment with tumor necrosis alpha-blocking agents attenuated the loss of kidney function. A study applying the tumor necrosis alpha-blocking agent etanercept in prevalent HD patients with hypoalbuminemia and inflammation showed an improvement in prealbumin levels, but the trial was marred by marked difficulties in recruiting patients conforming to the inclusion criteria, resulting in only 10 patients being randomized. Etanercept also decreased CV events, myocardial infarction, and stroke according to a meta-analysis in patients with rheumatoid arthritis, but the study did not consider kidney function.

Soluble TNF receptors are, in principle, inhibitors of TNF activity, but their serum levels are increased in CKD, and their concentration is inversely correlated with GFR. Both known types of soluble TNF receptors predict the progression of CKD. It remains unclear, however, whether soluble TNF receptors play a causative role in the progression of CKD or whether they are just inert markers.

According to more recent studies, TNF-α induced proinflammatory signaling in kidney mesangial cells, which was attenuated by the antioxidant resveratrol and kidney cell apoptosis. Both these studies seem to corroborate the role of TNF-α in the progression of kidney disease, which is further supported by experimental studies with TNF-α inhibition. Infliximab attenuated kidney fibrosis and urinary albumin/creatinine but did not impact creatinine clearance. In a rat model of induced insulin resistance, infliximab improved kidney concentration of inflammatory cytokines, insulin resistance, and kidney function parameters and enhanced the antifibrotic effect of the sodium-glucose cotransporter-2 (SGLT2) inhibitor empagliflozin. The association of soluble TNF with the progression of kidney disease was confirmed in a number of studies and a meta-analysis. Finally, TNF-α was also linked to a rise in the production of FGF-23.

Endothelin

Endothelins are strong vasoconstrictors, and their concentration increases in CKD. Endothelin-1, via activation of the endothelin-A (ETA) receptor, plays a deleterious role by increasing blood pressure and causing kidney inflammation, oxidative stress, vascular shear stress, arterial stiffness, endothelial dysfunction, and atherosclerosis. Vascular endothelin production in CKD may be attenuated by antihypertensive treatment. Kidney production of endothelin-1 is, however, only reduced by angiotensin receptor blockade, a mechanism that may contribute to the kidney protective effect of these drugs.

In experimental studies in CKD, specific blockade of the endothelin receptors reduced smooth muscle cell proliferation and increased endothelial capillary density. In a short-term randomized crossover study in CKD patients, endothelin-A receptor blockade resulted in decreases of plasma urate, ADMA, proteinuria, hypertension, and vascular stiffness. Doubts on the long-term use of these agents were, however, raised when 3 to 6 months of treatment were associated not only with a reduction of proteinuria but also with a rise in mortality due to fluid retention, however, maybe these problems could be overcome by using lower doses or more selective blockers. Nevertheless, in spite of the contradictory results of hard outcome studies, enough proof-of-concept data have been provided to point to endothelin as a compound with major negative biological impact.

More recently, endothelin-1 was, in experimental animal studies, identified as a genetic and epigenetic modifier of kidney fibrosis, an enhancer of kidney arteriolar contractility

and free radical accumulation in diabetic mice, and an inducer in mesangial cells of proliferation and extracellular matrix accumulation, hence worsening the course of diabetic nephropathy. Overexpression of human endothelin-1 causing long-term exposure in mice caused sustained hypertension and vascular and kidney injury. An independent clinical association with all-cause mortality and hospitalization was demonstrated in HD patients, as well as with hypertension and overall and kidney survival in autosomal dominant polycystic kidney disease. With regard to endothelin-A receptor blockade, one study showed an improvement of lipid profile in CKD patients. Experimental studies considering kidney function were contradictory. In a rat model of CKD and sleep apnea, hypertension was influenced positively, but not kidney dysfunction. On the other hand, in a rat model of type 2 diabetes with preexisting kidney disease, the progression of kidney injury was prevented especially with one specific blocker, atrasentan. Atrasentan also prevented podocyte injury induced by high glucose in vitro and diabetic mice. In a controlled study in patients with type 2 diabetes at high risk of ESKD selected to optimize efficacy and safety, those randomized to atrasentan were protected against kidney function decline. However, due to the early termination of the study, uncertainty remains about the long-term effect, while the selection procedure excluded a number of patients who would potentially have benefited. In spite of these matters of debate, the perception remains that endothelin-1 is an important compound in the pathogenesis of the uremic syndrome.

Fibroblast Growth Factor-23

The toxicity of FGF-23, a relative newcomer in the field of uremic toxicity research, has been reviewed in-depth previously. Originally, most information about this compound pointed to an observational association with hard outcomes but could not provide conclusive evidence whether this was a real toxin or merely a biomarker, but later data pointed to direct toxicity as well.

FGF-23 is a hormone that is mainly produced by osteocytes and osteoblasts. One of its main actions is to lower the hyperphosphatemia that normally occurs with progressive CKD via a reduction of tubular phosphate reabsorption and a decrease of $1,25(OH)_2$ vitamin D generation. In the course of CKD, plasma FGF-23 concentration starts rising early, very likely to compensate for the lack of capacity by the kidneys to excrete an adequate amount of phosphate. In addition, inflammation and iron deficiency can trigger a rise in FGF-23. The increase in phosphate excretion comes at the cost of a substantial number of negative effects. In a large number of observational clinical studies, FGF-23 was independently associated with an increased risk for CKD progression, CV events, and overall mortality. FGF-23 was also associated with cardiac hypertrophy, vascular damage, and endothelial dysfunction. Subsequently, a number of direct biological effects of FGF-23 were described, and the substance was shown to regulate intracellular calcium concentration and contractility of cardiomyocytes, kidney sodium handling decreasing tubular reabsorption potentially leading to hypervolemia, cardiac hypertrophy, and leukocyte recruitment upon infectious stimuli leading to enhanced infectious susceptibility.

More recent data suggest a role of FGF-23 in kidney cell carcinoma proliferation. However, mice in whom the production of bioactive FGF-23 was suppressed and who were fed a high-phosphate diet developed more important detrimental cardio-kidney effects than similarly treated normal mice, paradoxically suggesting a protective effect of FGF-23 in case of high phosphate load. Observational clinical studies indicated an association with incident, prevalent hypertension and a rising blood pressure in older adults, insulin resistance, risk of new-onset CKD and all-cause mortality in the general population, and carotid atherosclerosis in individuals without CKD, while a rise in serial FGF-23 values were linked to an increased risk for kidney replacement therapy. Inflammatory markers such as IL-1β, IL-6, TNF-α, or inflammatory markers at large were linked to an increase in the production of FGF-23. On the other hand, in an observational study, FGF-23 was directly correlated with fractional sodium excretion in CKD, negating a role in sodium retention and hypervolemia, and a mouse model of high FGF-23 without kidney damage, no association with CV disease was found.

Thus, in spite of a host of observational associations of FGF-23 with clinical outcome parameters, few experimental data point in favor of its toxicity, while some other experimental studies and some clinical studies suggest no or even a favorable effect.

Ghrelin

Ghrelin levels are definitely increased in CKD. Ghrelin is an orexigen playing a role in meal initiation and, as such, seems to oppose the trend for malnutrition of many CKD patients. However, the molecule has also been linked to several negative biological effects, such as: restricted insulin release and blunted insulin sensitivity, increases in triglyceride content in the liver, mitochondrial oxidative enzyme activities, anxiogenic response to stress, increase in serum corticosterone levels, release of growth hormone, and increases in sodium reabsorption. Ghrelin also has been linked to a rise in cardiac index and stroke volume index.

Clinically, low ghrelin levels have been associated with inflammation and CV risk in HD patients. On the other hand, ghrelin correlated negatively with body mass index. In peritoneal dialysis (PD), patients weight gain over time was associated to a decrease of ghrelin levels. In another study, ghrelin levels were inversely correlated with nutritional markers, suggesting increases in ghrelin at low dietary intake. The acute response to oral feeding in CKD was, however, markedly blunted versus controls. A possible explanation for the seeming paradox between uremic malnutrition and elevated ghrelin can be found in the observation that ghrelin is present in two forms, orexigen acylated ghrelin and desacylated ghrelin, which induces a negative

energy balance by decreasing food intake and gastric emptying. The balance between these two forms has repeatedly been shown to be disrupted in CKD, with more prominent retention of desacyl ghrelin. Plasma desacyl ghrelin was significantly higher in anorexic HD patients than in their nonanorexic counterparts.

More recent studies confirmed the role in sodium reabsorption, disclosing a number of mechanisms via protein kinase A and microtubule polymerization, and showed modifications in podocyte function and survival that could possibly play a role in kidney injury, especially in obesity. A clinical observational study showed ghrelin to be associated with inflammatory and nutritional, as well as with cardiac and vascular dysfunction parameters. Desacylated ghrelin was a marker of protein wasting in children with CKD, but another study found no association between total ghrelin and protein energy wasting (PEW) in dialyzed children. Ghrelin receptor antagonism improved angiotensin II–dependent hypertension in rats by creating a negative sodium balance. On the other hand, in an RCT in hemodialyzed patients, a ghrelin receptor agonist increased insulin growth factor 1, a surrogate endpoint with the potential to increase body mass and combat PEW, although a direct impact on clinical outcomes still needs to be demonstrated.

Immunoglobulin Light Chains

Although typical for multiple myeloma and other hematologic malignancies, the concentration of immunoglobulin light chains is also above normal in patients with CKD not suffering from those conditions. These molecules have been depicted as markers of inflammation but possibly also as pathogenetic factors. Experimental studies applying immunoglobulin light chains at concentrations as observed in CKD demonstrated that they decreased not only polymorphonuclear glucose uptake and chemotaxis but also leukocyte apoptosis, a factor possibly contributing to chronic inflammation. After their filtration by the glomeruli, immunoglobulin light chains are incorporated via the cubilin receptors into the kidney proximal tubular cells, where they are catabolized and tend to accumulate if the system is overloaded, to cause morphologic changes and kidney injury, be it essentially at the extremely high concentrations of hematologic malignancies. Their toxicity may be further enhanced by glycosylation. In observational studies in CKD, their concentration has been associated with inflammation and vascular calcification in one study and mortality in another.

Modified Lipids and Lipoproteins

The relationship between lipids, lipid metabolism, and lipoproteins on one hand and CKD on the other is complex. Modifications of lipid and lipoprotein metabolism can induce or accelerate the causes of CKD and CKD per se, but CKD also modifies lipid metabolism. In addition, the uremic state also causes structural changes, e.g., by oxidation, with pathophysiologic changes in their functional properties, so that those modified molecules can be classified as uremic toxins. Oxidation modifies not only lipoproteins but also lipids, and next to oxidation, there are also other posttranslational lipid modifications at play. All such changes and their consequences are summarized in detail in review such as the review by Florens et al. (2016).

In brief, structural and functional modifications may affect almost all involved components, including LDL, HDL, and free fatty acids. They may be the result of different modification processes, including, but not limited to, carbamylation and oxidation. Most notably, HDL is transformed from an anti-inflammatory and vasculoprotective to a proinflammatory moiety linked to vascular damage. Functional changes attributed to these modified lipids and lipoproteins are linked to highly detrimental epiphenomena and complications of CKD, such as endothelial dysfunction, thrombogenicity, inflammation, and vasoconstriction of smooth muscle cells and thus also, not surprisingly, CV morbidity and mortality. Moreover, F2-isoprostanes, which are oxidative modifications of arachidonic acid, have been directly associated with the progression of CKD.

In more recent studies, carbamylation of HDL has been related to a decrease of the antiaggregant properties of this compound. Another study confirmed the proinflammatory properties of uremic HDL, which was in part related to a decrease of polymorphonuclear leukocyte apoptosis. However, surprisingly, in a study of the impact of uremic HDL on cardiomyocytes, it appeared to be more protective against oxidative stress than genuine HDL from healthy subjects. In CKD, symmetric dimethyl arginine in dysfunctional HDL was shown to mediate glycocalyx breakdown.

In a case-control study, carbamylated HDL, but not carbamylated LDL, was independently associated with the progression of CKD in type 2 diabetes. Finally, ceramides, which play a pathophysiologic role in insulin resistance and cell apoptosis, are increased in CKD, independent of ischemic heart disease and preexistent established CV risk factors.

Neuropeptide Y

Neuropeptide Y, a known major orexigen, is retained in CKD. In PD patients, low neuropeptide Y levels are associated with anorexia. In the nervous system, neuropeptide Y inhibits the release of the neurotransmitter acetylcholine in nodose neurons. Neuropeptide Y also acts as a kidney vasoconstrictor by suppression of adenylate cyclase activity, a regulator of a wide array of cellular processes in vascular smooth muscle cells. Likewise, neuropeptide Y also inhibits cardiac adenylate cyclase, and the combination of high leptin, peptide YY, and neuropeptide Y, together with low ghrelin, has in the HD population been linked to hypertension, inadequate vasodilation, and cardiac hypertrophy and hence could predispose to CV events. In an observational study, neuropeptide Y predicted CV complications in ESKD.

In a more recent study, neuropeptide Y was associated with a higher risk for CKD and proteinuria and faster CKD progression.

Parathyroid Hormone

Disturbances in concentration of PTH, phosphate, and FGF-23 are strongly linked to each other, whereby changes in one factor impact the generation of the other, often following an adaptive response mechanism. The biological impact of PTH has extensively been studied and summarized and covers multiple aspects such as peripheral neuropathy, carbohydrate metabolism, hypertension, mitochondrial respiration, and cardiac hypertrophy. Yet, due to inherent PTH resistance in CKD, PTH levels need to be more elevated than with normal kidney function before generating an effect. In observational studies, both low and high PTH levels have been linked to increased mortality, with a more pronounced relationship for the low levels, which are linked to adynamic bone disease. Hence, the validity of PTH as a marker of bone turnover and generator of CV disease has been questioned. In two RCTs, PTH-lowering treatment with the calcimimetic cinacalcet did not impact the primary endpoints of these studies but influenced a number of surrogate endpoints such as vascular and cardiac valve calcification. In a secondary analysis of one of these two trials, the EValuation Of Cinacalcet Hydrochloride (HCl) Therapy to Lower CardioVascular Events (EVOLVE) study, cinacalcet appeared to lower FGF-23, and these reductions were linked to a lower number of CV events and death. As the rise in FGF-23 precedes the rise in PTH and serum phosphate, the question may be raised whether the rise in FGF-23 is not the primary pathophysiologic event preceding the development of secondary hyperparathyroidism. However, FGF-23 neutralization with antibody in mice with kidney failure improved hyperparathyroidism but increased mortality. All data taken together, the pathophysiologic role of PTH in CKD cannot be supported unequivocally.

In more recent studies, PTH increased bone loss and vascular calcification in rats independently of high serum phosphate, upregulated fibronectin synthesis in rat glomerular cells with a possible link to glomerular sclerosis, and was responsible for premature thymic atrophy and immune aging, while FGF-23 was not. PTH induced apoptosis in aortic smooth muscle cells, an effect attenuated by resveratrol, and it was linked to osteoblastic transformation of endothelial cells as a step leading to vascular calcification.

In clinical studies, PTH was associated positively with alpha-klotho in men, but the relationship was negative in women. Additionally, it was associated nonlinearly with mortality in CKD, with the lowest number of fatalities in the second quartile, and intact PTH was also associated with atrial fibrillation in nondialyzed CKD.

Retinol Binding Protein

Retinol binding proteins (RBPs) are not only transporters of retinoids but also function as regulators of retinoid metabolism and disposition. They have extensively been studied in CKD and were repeatedly shown to be elevated, although levels do not correlate as well with GFR than cystatin C or β_2-microglobulin. Contradictory biological functions have been attributed to this molecule. On one hand, RBP has been shown to induce apoptosis and inflammatory reaction in human endothelial cells. On the other hand, RBP isolated from acute kidney failure patients inhibited polymorphonuclear cell function and apoptosis. Quite a number of observational studies in specific populations not necessarily suffering from CKD link RBP to CV disease, carotid intima thickness, metabolic syndrome, and obesity. Only a few observational studies assessed links of RBP with outcomes in specific populations suffering from CKD. In one study, serum levels were associated with components of metabolic syndrome. In a population of type 2 diabetics with and without CKD, serum RBP was, however, not related to carotid intima thickness. On the other hand, urinary RBP was inversely related to kidney function and CV risk factors and was also increased in proportion with the degree of kidney radiation damage in mice.

Summary

Similar to the two other large groups of uremic retention solutes, these data show that the middle molecules also have the capacity to affect a number of biological systems that contribute to uremic syndrome. All solutes discussed in this section were linked to CV damage; almost all of them were linked to inflammation and kidney damage. On the other hand, some up until now in this chapter hardly mentioned problems were linked to middle molecules, such as PEW, carcinogenicity, and susceptibility to infection (Table 2.5). Ghrelin impacted the largest number of systems, followed by β_2-microglobulin, IL-6, TNF-α, and PTH (Table 2.5).

Discussion

This review summarizes the current knowledge about the biological impact (toxicity) of the uremic retention compounds with the most extensively documented toxicity. From this analysis, it appears that there are a plethora of compounds that exert some degree of toxicity. We describe a selection of 24 compounds or groups of compounds out of an even more comprehensive review that covered in total eight groups and 63 individual solutes. Hence, the uremic syndrome is a multifactorial condition. It seems highly improbable that one day a "golden bullet" would be identified, of which the removal would solve the entire problem. We are rather confronted with groups of compounds depending on various characteristics (protein bound vs. not; high molecular weight vs. low; hydrophilic vs. hydrophobic; intestinally generated vs. not; secreted by the kidney tubules vs. not) that might be handled together when it comes to decreasing their concentration.

With regard to the affected systems, the largest amount of data seems to point to CV damage, inflammation, fibrosis, and neurotoxicity. All these findings underscore the

TABLE 2.5 Physiologic Mechanisms and Organ Systems Affected by the Middle Molecules

	β_2M	IL-1β	IL-6	IL-8	TNF-α	ET1	FGF-23	Gr	IgLC	Lip	NPY	PTH	RBP
Cardiovascular damage	X	X	X	X	X	X	X	X	X	X	X	X	X
Inflammation	X	X	X	X	X	X		X	X	X			X
Neurotoxicity	X							X			X	X	
Hematology			X										
Thrombogenicity										X			
Metabolic changes			X		X	X		X	X			x	
Insulin resistance		X			X		X	X		X		X	X
CKD-MBD	X											X	
Kidney damage (fibrosis)	X	X	X		X	X	X	X	X	X	X	X	
Itching	X												
Protein energy wasting			X		X			X					
Carcinogenicity				X			X						
Susceptibility to infection							X						

β_2M: β_2-microglobulin; *CKD-MBD*, chronic kidney disease–mineral and bone disorder; *ET1*, endothelin-1; *FGF-23*, fibroblast growth factor-23; *Gr*, ghrelin; *IgLC*, immunoglobulin light chains; *IL*, interleukin; *Lip*, lipids and lipoproteins; *NPY*, neuropeptide-Y; *PTH*, parathyroid hormone; *RBP*, retinol binding protein; *TNF-α*, tumor necrosis factor-α.

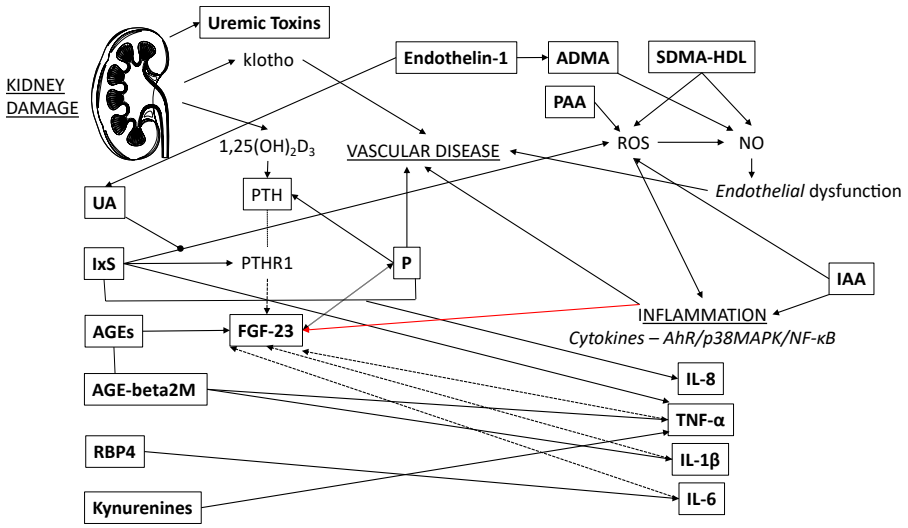
multifactorial disintegration of some of the key elements defining morbidity and mortality in the dialysis population and CKD at large, as the pathophysiologic processes induced by uremic toxicity start long before kidney replacement is needed. In addition, several of these systems influence each other (see Fig. 2.1). However, they may also have been assessed more frequently, hence leading to an underrepresentation of the other symptoms like itching or fatigue, although the latter is at least as important for the quality of life of CKD patients, a shortcoming that should be corrected in future research.

A direct effect on PEW was found rarely, but as such, several of the other frequently reported systems (inflammation, CV disease, neurotoxicity, infection) are an indirect cause of PEW.

RCTs are currently accepted to offer the highest level of evidence for a given impact. Although there are some RCTs on interventions to decrease the concentration of specific toxins, they are few, largely due to the low number of available interventional therapies that specifically can change the concentration of a given uremic toxin. In view of the multifactorial pathophysiology that can be understood from this and other reviews, one may wonder whether it makes much sense to consider further specific interventional trials to decrease one solute in the context of uremia, unless to offer proof of concept of toxic effects. In addition, such therapies are not always innocent. Allopurinol, e.g., may reduce uric acid, but any positive effect that is generated might be partially offset by its complications, such as Stevens–Johnson syndrome or leukocytopenia. Hence, it might be more useful to try to influence the concentration or metabolic impact of groups of molecules with similar characteristics and to underpin the utility of such approaches; we still remain in need of RCTs or, alternatively, observational studies with optimized correction for residual confounding. Observational studies might have an advantage on controlled studies by better mimicking real-life conditions in an area where many RCTs turned out negative at primary analysis for hard outcomes.

We believe that this chapter offers a useful reference work, giving a better insight into the complex picture of uremia with, in addition, an update of the data included in our 2018 review. At the same time, we hope it is a stimulus to fill in the gaps in the existing knowledge. It could also serve as a reference work for future uremic toxicity analyses and for selecting mechanisms for future drug development in the treatment of the uremic syndrome.

We demonstrate a kaleidoscopic picture of the most important compounds involved in defining the pathophysiologic process that ultimately results in the uremic syndrome. We summarize the biological/biochemical and clinical impact of 24 uremic retention solutes that have been assessed over the past half century and were classified previously as those most evidenced to have a biological impact. A complex picture (Fig. 2.2) emerges whereby almost all considered solutes affect several functions that contribute to the uremic syndrome and its complications, leading to increased morbidity and mortality of CKD. Of the affected mechanisms, especially the susceptibility to CV damage, inflammation and fibrosis appeared to be targeted, but these systems have presumably also been studied most extensively. In view of the apparently multifactorial nature of uremia, it seems illusory to think that decreasing the concentration of one solute will improve outcomes and probably attention should concentrate on decreasing the concentration of groups of solutes. More attention could be paid to quality of life aspects.



• **Fig. 2.2** Interference Among Uremic Toxins. *ADMA*, asymmetric dimethylarginine; *AGEs*, advanced glycation end products; *AGE-beta2M*, AGE-beta2microglobulin; *AhR/p38MAPK/NF-κB*, aryl hydrocarbon receptor/protein 38 mitogen-activated protein kinase/nuclear factor-kappa beta; *FGF-23*, fibroblast growth factor-23; *IAA*, indole acetic acid; *IL*, interleukin; *IxS*, indoxyl sulfate; *NO*, nitric oxide; *P*, phosphorus; *PAA*, phenyl acetic acid; *PTH*, parathyroid hormone; *RBP4*, retinol binding protein; *ROS*, reactive oxygen species; *SDMA*, symmetric dimethylarginine; *TNF*, tumor necrosis factor; *UA*, uric acid.

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3

Initiation of Dialysis Therapy

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Introduction

In the United States, the current prevalent population of adults with chronic kidney disease (CKD) exceeds 30 million individuals and continues to grow annually. Among this group are more than 740,000 individuals with kidney failure requiring treatment with renal replacement therapy, defined as the need for maintenance dialysis or kidney transplantation. Although the incidence rate for new kidney failure cases remained relatively stable in the first decade of the 21st century, the period from 2012 through 2017 once again saw a rise in the rate of new end-stage kidney disease (ESKD) cases. In 2017, the last year for which national data from the U.S. Renal Data System (USRDS) are available, over 120,000 individuals with kidney failure-initiated dialysis therapy with either in-center hemodialysis (HD), peritoneal dialysis (PD), or home HD. Due to this continued growth in incident cases, the overall population of patients treated with maintenance dialysis has more than doubled over the past 20 years. Additionally, given the continued growth in the prevalence of obesity and diabetes mellitus, the burden of kidney disease on health outcomes and health care expenditures is likely to continue to increase in the coming decades. Estimates from around the world indicate that growth in the United States is mirrored by similar growth in many other regions in the world, in particular Australia, Asia, and Western Europe. The true incidence of ESKD is less clear in developing countries, where the availability of dialysis technology and financial resources to pay for dialysis and related kidney care may be severely limited.

The period of time immediately preceding and following initiation of dialysis is one characterized by exceptionally high risk for adverse patient outcomes. In particular, the first 3 to 4 months following the start of dialysis has been shown to be characterized by an annualized mortality rate exceeding 40%. The transition period to dialysis therapy is also associated with high rates of other adverse outcomes, including heart failure exacerbations, all-cause hospitalizations, and new strokes. Patient-reported outcomes such as depression, anxiety, and fatigue may also worsen around the time of initiation of dialysis due to the large number of logistical hurdles that must be overcome and the psychosocial adjustment that must occur in the transition from medical management of advanced CKD to dialysis therapy. The appropriate timing of initiation of maintenance dialysis also has profound implications for the financial burden to health care systems—for Medicare beneficiaries, annual per-person per-year costs exceed $75,000 for PD and $90,000 for in-center HD. Thus, for multiple reasons, optimizing the transition to maintenance dialysis is a critical challenge facing the nephrologist and one that encompasses appropriate preparation of patients with CKD for dialysis, timely nephrology referral, appropriate dialysis modality selection, and determination of the best timing for dialysis initiation accounting for clinical and other patient-important factors. This chapter focuses on the indications, timing, modality selection, and process for initiation of dialysis in patients with advancing CKD.

Indications for Initiation of Dialysis in Chronic Kidney Disease Patients

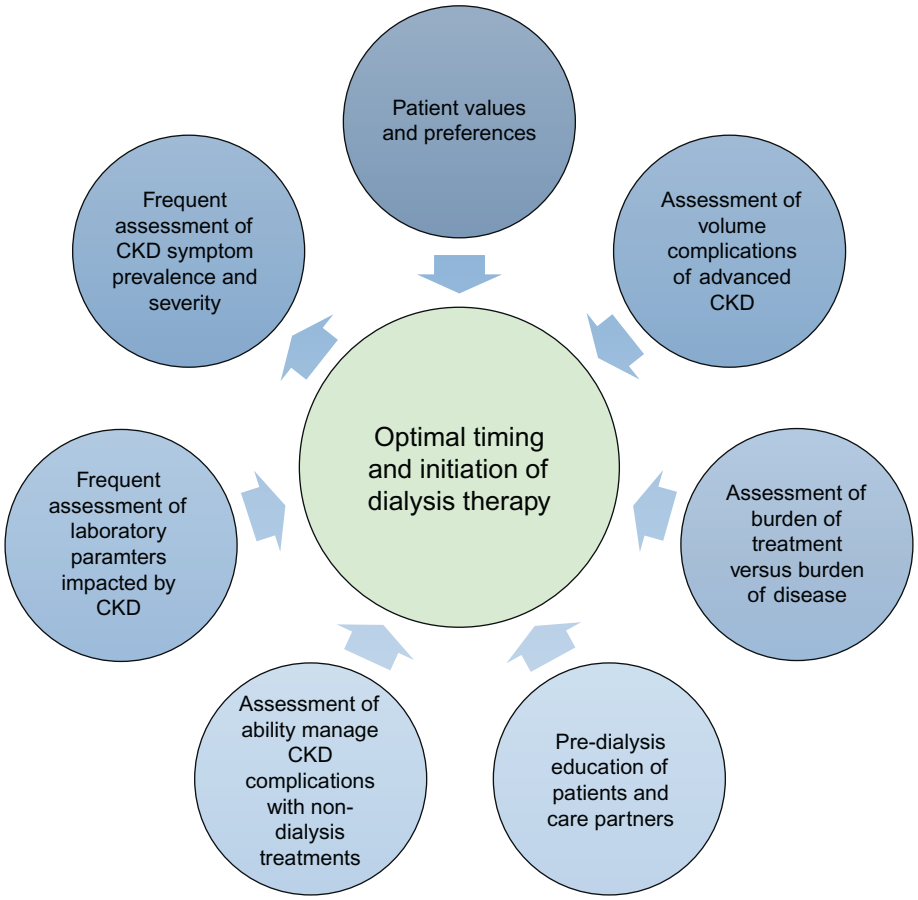
There has long been informal consensus among practicing nephrologists regarding true absolute indications for initiation of dialysis in patients with advanced CKD, largely severe manifestations of the uremic syndrome. Such absolute indications include uremic pericarditis, severe uremic encephalopathy, severe fluid overload leading to respiratory compromise and refractory to stepped diuretic therapy, and severe hyperkalemia refractory to medical management (Box 3.1). Uremic pericarditis, characterized by pleuritic chest or back pain, the finding of a pericardial friction rub, and often a pericardial effusion, has a poorly understood pathophysiology and no definitive diagnostic laboratory biomarker or imaging finding. Prompt initiation of frequent or intensified dialysis is the only treatment shown to be effective for the management of uremic pericarditis, with resolution noted in up to 50%–87% of cases. Early signs of uremic encephalopathy include nausea, restlessness, drowsiness, and slowing of concentration, memory, and executive function. Eventually, accumulation of uremic toxicity will result in myoclonus, asterixis, nystagmus, and obtundation. Regular assessment and physical examination to identify these advanced features are thus critical for patients with

• BOX 3.1 Absolute Indications for Dialysis Initiation Among Patients with Advanced Chronic Kidney Disease

1. Uremic pericarditis
2. Uremic encephalopathy with altered mental status
3. Recurrent or persistent hyperkalemia refractory to medical management
4. Severe fluid overload leading with pulmonary edema or impaired wound healing
5. Refractory nausea with vomiting
6. Severe uremic bleeding
7. Severe metabolic acidosis

advancing CKD, and recognition of any advanced features of uremic encephalopathy should prompt hospital admission and timely initiation of dialysis. Severe fluid overload leading to pulmonary edema and life-threatening hyperkalemia likewise require hospitalization for prompt dialysis therapy.

However, the majority of patients who reach kidney failure requiring initiation of renal replacement therapy do not require emergent dialysis for one of these life-threatening complications. Instead, decision making of timing and preparation for dialysis initiation for most patients with advanced CKD involves a complex integration by the treating nephrologist of clinical and laboratory parameters, symptoms attributable to the uremic syndrome, logistic issues centered on access to care, psychosocial factors, assessments of patients' coexisting illnesses and risk factors for decompensation without dialysis, and patient preferences (Fig. 3.1). Biochemical markers of filtration function include serum creatinine and blood urea nitrogen which are useful in assessing patients' progression toward the need for dialysis initiation, particularly when coupled with creatinine-based estimates of glomerular filtration rate (GFR); however, as discussed subsequently in greater detail, there remains no absolute threshold of GFR at which patients should be initiated on dialysis in the absence of other indications. Other important biochemical markers include markers of bone and mineral metabolism such as calcium, phosphorus, and parathyroid hormone; blood hemoglobin, ferritin, and iron saturation values, which can indicate worsening anemia and progressive loss of erythropoietin levels as a marker of loss of tissue mass; and increased serum potassium levels reflecting decreased filtration and distal tubular potassium secretary function. With the exception of refractory hyperkalemia, each of these other metabolic abnormalities is not an absolute indication for dialysis initiation but can be informative regarding trajectories of kidney function decline, provide



• Fig. 3.1 Example of a comprehensive patient-centered approach to decision making regarding preparation for and the timing of dialysis initiation. *CKD*, Chronic kidney disease.

challenges to nondialytic management, and together may help providers and patients work together to decide when to start dialysis. For example, severe hyperphosphatemia accompanied by hypocalcemia and secondary hyperparathyroidism may prompt consideration of activated vitamin D therapy or even calcimimetics, and if such therapy is unsuccessful in controlling these markers for a prolonged period of time, this may provide evidence that initiation of dialysis would benefit the patient from a renal osteodystrophy perspective. Such benefit, of course, would need to be weighed against the increase in treatment burden, cost, and complications associated with dialysis initiation.

Recently published data suggests that patients initiating dialysis due to refractory fluid overload has a significantly higher 12-month mortality and a greater risk for all-cause hospitalization and hospital readmission compared to patients initiating dialysis for other indications. While there is a paucity of data showing that earlier initiation of dialysis or other dialysis-related interventions may improve outcomes for this high-risk group, such data argue that close attention to volume-related complications is needed for these patients, and initiation of dialysis is a critical tool to be considered in managing refractory fluid overload in advanced CKD. At our center, we consider initiation of dialysis for advanced CKD when high doses of loop diuretics, such as torsemide 100 mg twice daily, are insufficient to control edema such that risk for skin breakdown or decreased patient mobility exists.

Identification of uremic symptomatology is a critical part of regular assessments by the nephrologist in the period of advancing CKD prior to dialysis initiation. Uremic pericarditis and true uremic encephalopathy have already been mentioned and are certainly absolute indications for dialysis initiation. Uremic pericarditis, manifested by a pericardial friction rub on examination and symptoms such as pleuritic or positional chest pain, arm pain, and back pain and sometimes accompanied by a pericardial effusion, should prompt hospital admission and rapid initiation of dialysis in the inpatient setting. High intensity of HD, typically daily treatment sessions until resolution of symptoms, should be considered. Similarly, true uremic encephalopathy, characterized by somnolence or obtundation in the presence of severe azotemia, should likewise prompt hospital admission for dialysis initiation. Such patients may be at high risk for further changes in mental status with dialysis initiation and should be monitored for the occurrence of the dialysis disequilibrium syndrome, discussed in greater detail later.

In addition to these clinical manifestations of the uremic syndrome, other signs and symptoms critical to assess in any patient approaching the need for dialysis include fatigue, lethargy, anorexia, loss of muscle or fat mass, sleep disturbances, bleeding tendency related to platelet dysfunction, memory or other neurocognitive dysfunction, pruritus, musculoskeletal pain, and sexual dysfunction. The accumulation of such signs and symptoms should prompt discussion among the patient, the nephrologist, and patient family members and caregivers to carefully weigh the pros and cons of dialysis initiation. Critically, there is no absolute number or severity of symptoms that necessarily should prompt dialysis initiation of every patient; instead, this assessment and decision making should be tailored to the individual patient and the individual clinical and social context. In some cases, patients may feel that a certain level of uremic symptom burden is acceptable, especially if nondialytic medical therapy is available and preferable over the burden of treatment associated with dialysis. Examples of nondialytic therapies include antiemetics such as ondansetron for the treatment of uremia-associated nausea, appetite stimulants for uremia-associated anorexia, and phosphate binders, ondansetron, naltrexone, or gabapentin for uremic pruritis. In other cases, shared decision making may lead to earlier initiation of dialysis due to valid concerns about medication burden, patient suffering, and family or caregiver support for close monitoring and symptom assessment in the home environment.

Adding to the complexity regarding the optimal timing of dialysis initiation based on uremic symptoms assessment is the uncertainty regarding which signs and symptoms of the uremic syndrome may improve or be ameliorated with the start of dialysis for each individual patient. Certainly, it is true that patients with advanced CKD prior to initiating dialysis have a wide variety and high burden of symptoms, and that these symptoms do prompt initiation of dialysis in many cases. However, a number of recently published studies have indicated that not only does dialysis treatment not eliminate all symptoms of the uremic syndrome but also that the number and severity of physical, mental, and emotional symptoms in patients with ESKD undergoing dialysis are not significantly different from those for patients with predialysis advanced CKD. Studies of patients with ESKD treated with maintenance dialysis have demonstrated a high prevalence of patient-reported treatment-related symptoms, including cramping, pruritus, insomnia, and fatigue. Certain complex symptoms, such as fatigue, are multifactorial in etiology and may be influenced by comorbid or associated illnesses such as anemia, depression, anxiety, sleep disturbances, and chronic pain. Thus, although fatigue is highly prevalent in predialysis patients with advanced CKD, it is similarly prevalent in ESKD patients undergoing maintenance dialysis and does not seem to be impacted by dialysis frequency or intensity. Similarly, although progressive CKD is associated with the appearance and worsening of cognitive impairment, there remains no good evidence that earlier initiation of dialysis impacts the severity or progression of cognitive difficulties and dysfunction. For example, in the Choices for Health Outcomes in Caring for ESKD (CHOICE) study, 26% of incident dialysis patients had worsening in self-reported cognitive difficulties 1 year after dialysis initiation compared to only 17% of patients reporting an improvement in cognitive function. Additional challenges are that many patients may downplay symptoms or may adapt to chronic symptoms or a lower level of physical functioning over time. That is not to say that dialysis does not improve certain classic constituents

of the uremic syndrome, in particular anorexia, nausea, and vomiting. However, physicians should incorporate realistic expectations regarding dialysis-related symptoms into conversations with patients regarding preparing for dialysis initiation. Patients should be informed that dialysis may or may not alleviate all of their uremic symptoms and may or may not result in improvement in energy and functional status.

As a further challenge for the nephrologist in monitoring patients progressing toward the need for renal replacement therapy, there is currently no widely adopted and validated symptom assessment patient-reported outcome measure (PROM) or tool for assessment of uremic symptoms. A number of survey instruments assessing symptoms among prevalent dialysis patients have been developed, including the Dialysis Symptom Index (DSI), the modified Edmonton Symptom Assessment System (ESAS), and most recently, the Symptom Monitoring in renal Replacement Therapy–Hemodialysis (SMaRRT-HD) questionnaire. Additionally, the established standard for assessment of health-related quality of life (HRQOL) among dialysis patients, the Kidney Disease Quality of Life 36-item short form survey (KDQOL-36), does contain a symptom/problem subscale that can be used to track common symptom severity among dialysis patients. None of these instruments, however, has been widely validated among patients with advanced-stage 4 or 5 CKD who are approaching but have not yet required initiation of renal replacement therapy. Thus, assessment of uremic symptom burden, frequency, and severity for patients with advanced CKD in the current era is typically accomplished by the individual nephrologist in the course of routine office or telemedicine visits. However, further research is needed to establish best practices for uremic symptom assessment and incorporation into clinical decision making.

The central task of the nephrologist in assessing the optimal timing of renal replacement therapy for patients with advanced CKD is thus to balance the adverse consequences and impact of untreated kidney failure with the potential risk and treatment burden associated with initiation of maintenance dialysis. Excessive delay in the initiation of dialysis may lead to recurrent hospital admission for metabolic and volume complications of kidney failure, including hyperkalemia, pulmonary edema, and uncontrolled hypertension. Delay in dialysis may also expose patients to prolonged periods of protein-energy wasting, malnutrition, and uremia-related weight loss. Conversely, excessively early initiation of dialysis may expose patients unnecessarily to complications of the dialysis procedure itself, including infection-related risk from arteriovenous (AV) dialysis access, hemodynamic fluctuations related to ultrafiltration with subsequent myocardial stunning, and regional alterations in cerebral perfusion, and excess oxidative stress. Additionally, the requirement for daily or thrice weekly in-center or home dialysis treatments will have substantial effects for patients' ability to work, travel, and function independently and may adversely impact HRQOL.

Clinical Practice Guidelines for Initiation of Dialysis

Given the inherent challenges in the assessment of the optimal time for dialysis initiation in a patient with progressive and advanced CKD, numerous clinical practice guidelines have been published over the past two and half decades to provide individual practicing nephrologists with guidance in the management of patients during this high-risk transition.

Past Recommendations for Timing of Initiation of Dialysis

Prior to 1997, when the National Kidney Foundation Dialysis Outcomes Quality Initiative (DOQI, now KDOQI) released its first comprehensive clinical practice guidelines for dialysis adequacy, there was no clear consensus regarding the optimal timing of dialysis initiation in patients with advanced CKD. In the 1990s, a number of observational research studies had shown a strong correlation between markers of protein-energy wasting and adverse outcomes such as increased mortality risk. It was also observed that objective measures of protein intake, such as the normalized protein catabolic ratio (nPCR), increased over the first 6 months after dialysis initiation, with the presumption that these changes reflected amelioration of uremic toxicity. Thus, when the KDOQI work group on dialysis adequacy released its recommendations in 1997, the specific guidelines commenting on the timing of dialysis initiation focused primarily on rigorous assessment of malnutrition and protein intake. Specifically, the group recommended that patients with advanced CKD should be advised to initiate some form of dialysis when the weekly renal Kt/V_{urea} fell below 2.0, unless either edema-free body weight is stable, the nPCR is greater than or equal to 0.8 g per kilogram of body weight per day, or if there is an absence of clinical signs or symptoms attributable to uremia (Table 3.1). The threshold of renal Kt/V_{urea} of 2.0, which corresponds to a threshold of estimated GFR of approximately 10.5 mL/min/1.73 m^2, was initially selected based on expert opinion, with supportive evidence over the subsequent decade extrapolated from the findings of two large studies of patients treated with PD: the Canada-USA (CANUSA) study and the Adequacy of PD in Mexico (ADEMEX) trial. Although, the findings from CANUSA, a prospective multicenter cohort study of 680 incident PD patients, indicated that each 0.1-unit/week increase in weekly total Kt/V was associated with a 6% decrease in overall risk for death, the ADEMEX trial subsequently showed no difference in outcomes when patients were randomized to PD prescriptions resulting in weekly Kt/V values of approximately 1.8 versus 2.3.

In 2006, KDOQI updated its clinical practice guidelines for dialysis adequacy to reflect widespread adoption of serum creatinine–based equations for estimating GFR and removed the discussion of calculation of the weekly renal Kt/V_{urea} from the guidelines. Instead, the guideline stated that nephrologists should incorporate evaluation of the benefits,

TABLE 3.1 Past and Current National Kidney Foundation/KDOQI Clinical Practice Guidelines on the Timing of Initiation of Maintenance Dialysis for Patients with End-Stage Renal Disease

Year of Release	Statement
1997	Patients should be advised to initiate some form of dialysis when the weekly renal Kt/V_{urea} falls below 2.0, unless there is (1) stable or increased edema free body weight; (2) nPCR ≥ 0.8 g/kg/day; or (3) absence of clinical signs or symptoms attributable to uremia.
2006	Patients who reach CKD stage 4 (estimated GFR < 30 mL/min/1.73 m2) should receive timely education about kidney failure and options for its treatment, including kidney transplantation, PD, HD in the home or in-center, and conservative treatment. Patients' family members and caregivers also should be educated about treatment choices for kidney failure.
	Estimation of GFR should guide decision making regarding dialysis therapy initiation. GFR should be estimated by using a validated estimating equation (Table 1) or by measurement of creatinine and urea clearances, not simply by measurement of serum creatinine and urea nitrogen.
	When patients reach stage 5 CKD (estimated GFR < 15 mL/min/1.73 m2), nephrologists should evaluate the benefits, risks, and disadvantages of beginning kidney replacement therapy. Particular clinical considerations and certain characteristic complications of kidney failure may prompt initiation of therapy before stage 5. Such complications include otherwise unexplained decline in functioning or well-being; gastrointestinal dysfunction; or weight loss or other evidence of malnutrition.
2015	Patients who reach CKD stage 4 (GFR < 30 mL/min/1.73 m^2) should receive education about kidney failure and options for its treatment, including kidney transplantation, PD, HD in the home or in-center, and conservative treatment. Patients' family members and caregivers also should be educated about treatment choices for kidney failure.
	The decision to initiate maintenance dialysis in patients who choose to do so should be based primarily upon an assessment of the signs and/or symptoms associated with uremia, evidence of protein-energy wasting, and the ability to safely manage metabolic abnormalities and/or volume overload with medical therapy rather than on a specific level of kidney function in the absence of such signs and symptoms.

CKD, Chronic kidney disease; *GFR*, glomerular filtration rate; *HD*, hemodialysis; *KDOQI*, Kidney Disease Outcomes Quality Initiative; *nPCR*, normalized protein catabolic ratio; *PD*, peritoneal dialysis.

risk, and disadvantages of initiation of renal replacement therapy when patients reach stage 5 CKD, corresponding to an estimated GFR of 15 mL/min/1.73 m^2 (see Table 3.1). An substantial additional change to the guideline was a recommendation that certain clinical considerations or complications may prompt initiation of renal replacement therapy *before* stage 5, including a decline in patient functioning or well-being, gastrointestinal dysfunction, or weight loss. The 2006 update, therefore, represented a liberalization of recommendations vis-a-vis dialysis initiation in patients with advanced CKD, placing this decision within the realm of the subjective assessment and clinical judgment of the practicing nephrologist, with little objective data to guide such decision making.

The Initiating Dialysis Early and Late (IDEAL) Trial

Clinical practice guidelines for dialysis initiation practices published through the end of the 20th century were largely based on consensus and expert opinion, with little contribution from research data. In the last years of the 20th century and first decade of the 21st century, a number of observational studies were conducted to investigate the association of estimated GFR at the start of maintenance dialysis with subsequent clinical outcomes. The results of these studies, in general, supported the hypothesis that a higher estimated GFR at the time of dialysis initiation, when calculated using serum creatinine-based estimating equations, was associated with a higher risk for adverse outcomes. Interestingly, a smaller number of studies estimating GFR via timed urine collections and urinary creatinine clearances found no association between GFR at dialysis initiation and subsequent outcomes. These seemingly conflicting results raised concerns among many investigators regarding the influence of residual confounding on observed relationships between estimated GFR and dialysis initiation outcomes. In particular, there emerged concern that since serum creatinine–based estimating equations are subject to misclassification error in patients with substantial sarcopenia, the observed relationships between higher estimated GFR at dialysis start with higher mortality may, in actuality, represent an association of sarcopenia with adverse outcomes.

In light of persistent uncertainty regarding the benefit of using estimated GFR in patients with advanced CKD to time dialysis initiation, and in the absence of other objective measures of kidney function on which to base this critical clinical decision, the publication of the Initiating Dialysis Early and Late (IDEAL) trial in 2010 was a landmark event in nephrology. The IDEAL trial was the first, and to date remains the only, large randomized clinical trial to test the effect of estimated GFR at the time of dialysis initiation

on subsequent clinical outcomes. The IDEAL trial, conducted between July 2000 and November 2008, enrolled 828 adults with advanced CKD, defined as an estimated GFR of less than 15 mL/min/1.73 m^2 body surface area, from 32 centers in Australia and New Zealand. Enrolled patients were randomized to initiating dialysis at an estimated GFR of 10–15 mL/min/1.73 m^2 (the "early start" group) or an estimated GFR of 5–7 mL/min/1.73 m^2 (the "late start" group). Patients were followed for a median of 3.6 years for occurrence of death (the primary outcome), cardiovascular events, and hospitalization and were also assessed on metrics of HRQOL. Disappointingly, for many nephrologists who had eagerly awaited the results of IDEAL, the primary finding from the study was that there were no significant differences between the randomized groups in the incidence of any of the primary or secondary outcomes.

What Has Happened Since IDEAL?

Soon after the publication of the IDEAL trial, a number of important limitations of the study results were noted by observers that should be considered when interpreting the study findings for implementation in clinical practice in the United States. First, among patients randomized to the early start group, approximately 20% initiated dialysis with an estimated GFR of less than 10 mL/min/1.73 m^2. Conversely, among those patients assigned to the late start group, over 75% initiated dialysis with an estimated GFR greater than 7 mL/min/1.73 m^2. The effect of these "crossover" protocol deviations was that the mean difference in estimated GFR at dialysis initiation when comparing the two randomized groups was only 2.2 mL/min/1.73 m^2. A second limitation of the IDEAL trial pertains to generalizability to the population of individuals with kidney failure treated with dialysis in the United States. As the IDEAL trial was conducted in Australia and New Zealand, the majority of patients were white, with a lower burden of coexisting illnesses compared to the typical patient with ESKD in the United States. Furthermore, over half of IDEAL participants were treated with PD as their initial dialysis modality; most had a long-standing relationship with a nephrologist, and few patients treated with in-center HD initiated dialysis via a central venous catheter. These characteristics contrast sharply with those of the incident dialysis population in the United States, where nearly 90% of patients initiate in-center HD, and around 80% of patients initiate dialysis via a central venous catheter. However, notwithstanding these limitations, the results of the IDEAL trial have profoundly influenced the clinical practice and clinical practice guidelines for the care of patients with advanced CKD in the United States.

Since the publication of the IDEAL trial now over a decade ago, there have been no subsequent randomized controlled trials evaluating the benefit of initiation of dialysis at higher versus lower levels of estimated GFR. A number observational cohort studies have been conducted in efforts to overcome some of the limitations of the IDEAL trial and take advantage of increasingly large and robust clinical cohorts and administrative registries. Furthermore, other observational studies have assessed whether the potential impact of timing of dialysis initiation based on estimated GFR may be modified based on clinical or patient characteristics, such as planned or actual dialysis modality or comorbid conditions such as diabetes mellitus. Unfortunately, despite substantial investment of time and resources, the results of these follow-up studies have not challenged the primary null finding of the IDEAL trial. There thus remains no compelling evidence that the use of estimated GFR in decision making on the timing of dialysis initiation results in improvement in patient-centered outcomes for individuals with advanced CKD approaching the need for renal replacement therapy.

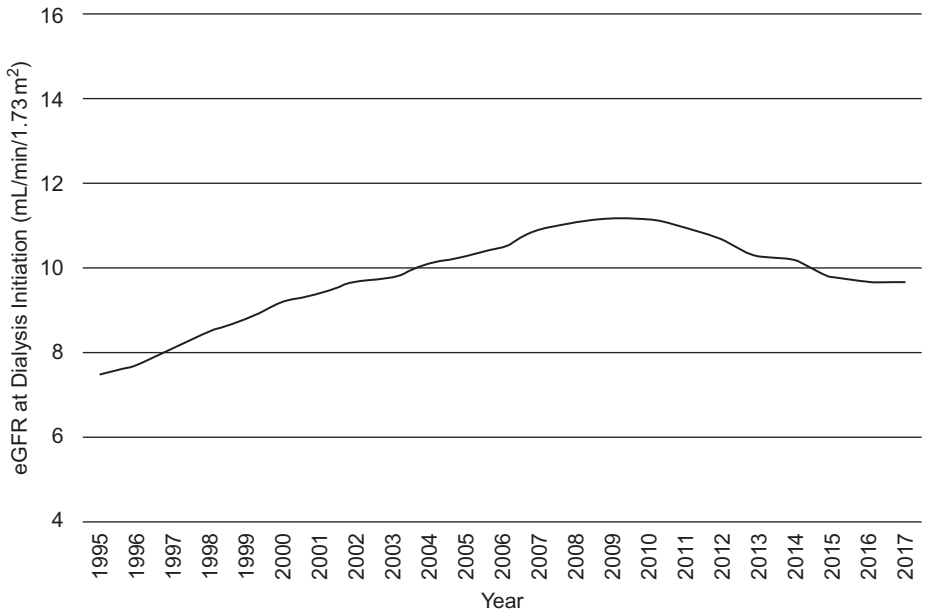
Current Recommendations for Timing of Initiation of Dialysis

The most recent iteration of the KDOQI clinical practice guidelines for HD adequacy was published in 2015 and contain recommendations for practicing nephrologists regarding decision making for the timing of dialysis initiation that reflects an integration of the evolution of prior clinical practice guidelines with lessons learned from the IDEAL study. The latest KDOQI guidelines state that rather than focusing on a specific level of kidney function as defined by the estimated GFR, clinicians should base the decision to initiate dialysis primarily on an assessment of complications of kidney failure, including signs and symptoms of uremia, protein-energy wasting, or metabolic or volume disturbances that are unresponsive to maximal medical therapy (see Table 3.1).

We believe that the most recent KDOQI clinical practice guideline represents the most up-to-date and patient-centered approach to clinical decision making around dialysis initiation timing. Such an approach should incorporate a broad assessment of each patient's clinical status that includes assessment of signs and symptoms of uremia, a review of absolute levels and trends of biochemical markers of metabolic complications of advanced kidney disease, physical exam findings of fluid accumulation, and an in-depth incorporation of each patient's values and preferences regarding tradeoffs of living with the burden of untreated kidney failure versus the burden of initiation of dialysis therapy. Ultimately, nephrologists should employ the principles of shared decision making while seeing and frequently assessing patients with advanced CKD, ensuring that the decision of whether and when to start dialysis is patient and family centered.

Trends in Timing of Initiation of Dialysis

Accompanying the evolution of clinical practice guidelines for dialysis initiation in the United States over the past two decades have been changes in dialysis initiation practices in this country as manifested by trends in the estimated GFR



• **Fig. 3.2** Trends in estimated glomerular filtration rate *(eGFR)* at initiation of dialysis in the United States, 1995–2017. Adapted from U.S. Renal Data System Annual Data Reports from 2007, 2010, 2013, 2015–2017.

at initiation of dialysis. From the mid-1990s through 2009, the mean estimated GFR at dialysis initiation for patients with incident ESKD rose from 7.7 mL/min/1.73 m^2 to 11.2 mL/min/1.73 m^2 (Fig. 3.2). The reasons for this secular trend prior to 2010 are not entirely clear, although they may have been influenced by the changing demographic characteristics of the dialysis population, implementation of automated estimated GFR reporting by laboratory facilities, and changes in predialysis practice patterns such as duration of prenephrology care. In 2010, incidentally, the same year that the IDEAL trial was published, there was an inflection point in long-term secular trends such that over the subsequent 5 years, the mean estimated GFR at dialysis initiation declined to approximately 10 mL/min/1.73 m^2. The reasons for such changing trends are likely numerous and complex, although the influence of the IDEAL trial results has very likely at least contributed in part, as have the changing clinical practice guidelines mentioned earlier in this chapter.

Preparation for Renal Replacement Therapy

Predialysis Chronic Kidney Disease Education

A critical component of the care of patients with CKD is appropriate and timely provision of dialysis-related education in advance of initiation of dialysis treatment. Such dialysis-related education should generally begin when patients reach stage 4 CKD (estimated GFR 15–30 mL/min/1.73 m^2), although it may be provided at earlier stages of CKD depending on factors such as access to regular nephrology care, rate of GFR decline, and patient preferences. Dialysis-related education should include teaching related to the spectrum of options for renal replacement therapy, including home dialysis modalities (PD and home HD), preemptive kidney transplantation, and maximum conservative (nondialytic) treatment of advanced kidney disease. Additionally, education should provide information on permanent dialysis access options, including PD catheters for patients considering PD and arteriovenous fistulas (AVFs) and grafts (AVGs) for patients considering in-center or home HD. The overall goal for CKD education is to prepare patients and families in advance of the need for renal replacement therapy so that patients feel informed, respected for their values and preferences, and empowered to make decisions regarding treatment for kidney disease that is patient and family centered. Realistically, such CKD education cannot happen merely over a single educational session, but rather concepts and teaching points may need to be repeated and reinforced multiple times for patients and care partners to achieve optimal retention and decisional support. Research assessing the impact of CKD patient education programs has shown that such programs are associated with a higher uptake of home dialysis modalities, greater objective and self-reported knowledge of renal replacement therapy options, and may improve survival and HRQOL following dialysis initiation.

Timing of Dialysis Access Placement

A central consideration in the care of a patient with advanced CKD approaching the need for dialysis is the timely placement of a permanent dialysis access. Over the past three decades, a large body of literature has robustly demonstrated that the use of central venous catheters in incident and prevalent HD patients are associated with a higher risk of adverse clinical outcomes compared to the use of AVFs or

AVGs. These adverse outcomes include a greater burden of infection-related morbidity, a higher risk of hospitalization, and higher rates of cardiovascular events and all-cause mortality. Despite this body of literature and clinical practice guidelines stating that all patients should have functional permanent dialysis access at the initiation of dialysis therapy, approximately 80% of patients initiating HD in the United States use a central venous catheter rather than a permanent AV access.

For patients who choose in-center or home HD, the optimal solution is placement of an AVF at least 6 to 9 months prior to the anticipated need to initiate dialysis, with the goal to allow adequate time for AVF maturation and potential for assisted maturation with access interventions and/or revision or even new access placement if needed. Contemporary reports have documented primary AVF failure rates ranging from 20% to 60%, with wide variation depending on patient age and comorbid prevalence of diabetes and cardiovascular disease. If preoperative imaging or surgeon assessment reveals inadequate size vasculature or anatomy for placement of a native AVF, then an AVG should be placed at least 6 weeks prior to initiation of dialysis to allow for healing. Many AVGs, however, can be used sooner than this conservative estimate.

For patients who choose treatment with PD, the PD catheter should be placed ideally at least 2–4 weeks prior to the anticipated need for initiation of dialysis to allow adequate time for healing and prevent the incidence of pericatheter leaks and infection. Depending on local availability of surgeons with experience in PD catheter placement, arranging for surgery consultation and PD catheter placement within 1–2 weeks of the decision to initiate dialysis may be limited. An alternative strategy that allows for more advanced preparation is to implant a PD catheter far in advance of the anticipated need for dialysis and then embed the exterior portion of the catheter under the skin in the subcutaneous space of the abdominal wall. Then, when the clinical need for dialysis initiation arises, this embedded portion can be externalized via a short office procedure, and full volume PD can be initiated immediately without additional time needed for tract healing. A number of studies have demonstrated that PD catheters can be embedded for prolonged periods, even years, and still reliably result in functional PD when externalized. Finally, the past decade has seen a growth in the initiation of so-called "urgent start PD," in which a patient who has unexpectedly progressed to kidney failure is treated with PD within a few days following catheter placement. With urgent start PD, exchanges are performed with the patient in a supine position, and low dialysate volumes are used, typically 750 mL to 1.5 L, to reduce intra-abdominal pressure and prevent pericatheter leaks as the surgical site and catheter track heal. During these low-volume supine exchanges, PD training can occur for the patient and any care partners, such that within 14–21 days, patients can transition home and start full volume PD without any intervening period of HD.

Dialysis Modality Selection

As discussed previously, early predialysis patient and care partner education is a critical part of the management of advanced CKD, and a key component of this education is discussion and decision making regarding treatment modalities for chronic kidney failure. Treatment modality selection should incorporate not only person-centered shared decision-making principles, such as respect for patient values and preferences, but also clinical appropriateness and local availability of expertise and resources. Options for dialysis modalities, including in-center HD, PD, and home HD, are discussed next.

In-Center Dialysis Modalities

Conventional In-Center Hemodialysis

In the United States, despite recent growth in the adoption of home dialysis modalities, greater than 85% of all patients with incident kidney failure are treated with conventional in-center HD. The vast majority of these patients are treated three times weekly for between 3.5 and 4.5 hours per session. A typical HD prescription includes a polysulfone or other synthetic high flux dialyzer, blood flows between 300 and 450 mL/min, and dialysate flows of between 500 and 800 mL/min. Dialysate electrolyte composition will generally include a potassium concentration of 2 or 3 mEq/L, a calcium concentration of 2.5 or 3 mEq/L, and a bicarbonate concentration of 30 to 35 mEq/L. Dialysate electrolyte concentrations should be individualized for each patient based on the extent of residual kidney function at dialysis initiation, as well as patient adherence and dietary factors.

When HD is first initiated, some nephrologists choose to start with one to three dialysis sessions of shorter than conventional duration and with lower blood and dialysate flows to reduce rapid blood solute clearance and to prevent the occurrence of the dialysis disequilibrium syndrome. An example of such a strategy would be to prescribe a first treatment of 2 to 2.5 hours in duration at a blood flow rate of 200 mL/min, with the next session increasing in duration to 2.5 or 3 hours, with a blood flow rate of 250 to 300 mL/min. It should be noted that although this approach makes physiologic sense, there are no contemporary studies linking the practice of "gentle" dialysis initiation with a reduced incidence of the dialysis disequilibrium syndrome or other adverse clinical outcomes.

Incremental In-Center Hemodialysis

Although, as mentioned previously, most patients initiating HD in-center are treated three times weekly, some patients with substantial residual kidney function may be treated using an approach termed "incremental" HD. With this approach, patients are treated with less intensive HD regimens, typically of shorter duration and/or less frequency, guided by frequent assessment and monitoring of changes in patients' residual kidney function. There have been no

randomized clinical trials showing improvement in clinical outcomes among incident HD patients treated with an incremental approach, although for many patients, there may be improvements in HRQOL with minimizing weekly HD session frequency or total duration. In addition, a theoretical benefit is preservation of residual kidney function, although this association has been shown only in retrospective observational studies.

Home Dialysis Modalities

Peritoneal Dialysis

Over the past decade, there has been remarkable growth in the utilization of home dialysis modalities in the United States, and the vast majority of this growth in terms of absolute numbers has been in the increased use of PD. In 2008, less than 7% of the prevalent dialysis population was treated with PD, and by 2017, this percentage had grown to exceed 10%. For many patients, PD has the potential to enhance patient centeredness of care through enhancing autonomy, independence, self-care, and flexibility in work and travel schedules. Additionally, PD presents a lower overall per-patient cost to the health care system. Thus, all medically eligible patients with advanced CKD should be educated and informed about options for PD (and also home HD). There are a variety of forms of PD, with automated PD (APD) and continuous ambulatory PD (CAPD) being the most common. Initial dialysis prescriptions for PD should incorporate the patient's body size as well as residual kidney function in deciding on the volume and number of daily exchanges. Typical initial dwell volumes range from 1.5 to 2.5 L, and for patients initiated on dialysis via CAPD, the number of dwells per day is typically four. For patients treated with APD initially, many patients with substantial residual kidney function may be able to be treated with nocturnal PD only, with no last fill, resulting in a "dry day." After initiating PD, the PD prescription should be adjusted based on regular assessment of patient symptom burden, degree of metabolic and volume control, and to achieve adequate solute clearance. Baseline peritoneal membrane transport characteristics should be established after initiating PD, typically 1–2 months following dialysis initiation.

As for patients starting in-center HD, consideration should be given for initiation of incremental PD in individuals with significant residual kidney function at the start of dialysis therapy. Incremental PD can be delivered using a number of different strategies, including administering treatments at a frequency of less than daily, by delivering fewer daily exchanges, or by using lower fill volumes than a conventional prescription. It should be noted that no high-quality evidence exists to demonstrate that the use of an incremental PD strategy either improves or worsens symptoms or other clinical outcomes for patients with incident chronic kidney failure, but such a strategy may reduce treatment-related burden for patients.

Home Hemodialysis

Similar to the growth in PD in the United States over the past decade, the adoption of home HD has grown and, in fact, has seen a larger proportional growth than any other dialysis modality over the past 15 years. Multiple factors have contributed to this large growth, including enhanced person-centered delivery of predialysis CKD education, a growing body of literature supporting equivalent outcomes among patients treated with home HD compared to in-center HD, and perhaps most importantly, the advent of easier-to-operate home HD equipment. Although some patients treated with home HD utilize conventional HD equipment and a trained dialysis helper, a growing percentage of patients who choose to pursue home HD therapy are treated with short daily HD four to six times weekly using a low dialysate volume approach. Shorter dialysis sessions, often 2–3 hours in duration, can allow patients to achieve maximum flexibility incorporating dialysis treatments into their daily life schedules. Although the majority of prevalent home HD patients were initially treated with conventional in-center HD, with optimal planning, advanced AV access placement, and patient education, patients can initiate dialysis directly with home HD without an intervening period of treatment with another modality.

Conclusions

The past decade has seen continued growth in the population of incident dialysis patients in the United States. The optimal timing of dialysis initiation in patients with incident chronic kidney failure remains unknown, and recent clinical practice guidelines have stressed that decision making around the start of dialysis should be person centered and collaborative, with a focus on alleviating symptoms and metabolic and volume complications arising from untreated CKD. Numerous options exist for dialysis therapies for patients with incident kidney failure, and these include in-center HD, PD, and home HD, as well as incremental treatment with each of these modalities. The proportional use of home dialysis modalities among incident dialysis patients in the United States has grown significantly over the past 10 years, and this trend is likely to continue into the next decade. This growth is multifactorial and includes contributions from changing payment and policy priorities and growing recognition that home dialysis may enhance person-centeredness of care through promotion of independence, autonomy, and patient self-care.

Acknowledgments

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An important randomized trial showing no significant benefit of increased small solute clearance beyond that typically achieved in clinical practice among PD patients.

Robinson BM, Zhang J, Morgenstern H, et al. Worldwide, mortality risk is high soon after initiation of hemodialysis. *Kidney Int.* 2014;85(1):158–165.

Important study showing the period of time immediately following initiation of dialysis (first 120 days) is associated with high risk of adverse clinical outcomes.

SECTION 2

Hemodialysis

4

Urea Kinetic Modeling for Guiding Hemodialysis Therapy in Adults

ALONSO R. DIAZ, MD • ANDREW I. CHIN, MD

Introduction

Dialysis is arguably a successful life-sustaining therapy. This unique, extracorporeal therapy has granted millions of people years of life after kidney failure. Hemodialysis (HD) is presently the most utilized form of renal replacement therapy around the globe. Even as technology improves, the method through which HD provides its therapy remains little changed over the last few decades. The removal of low-molecular-weight, water-soluble, and minimally protein-bound substances primarily by diffusion is still what dialysis does best.

Clinicians order HD as a prescription. Like any medication prescription, the timing, frequency, and dose are all important to the efficacy of the treatment. Nephrologists should assess the dose of HD they are prescribing by periodically measuring it. The dose of HD is the fractional clearance of urea, often referred to as the adequacy of HD. Meeting a minimum threshold for urea clearance cannot be the only metric for an adequate HD treatment. Thorough consideration of other objective and subjective factors also becomes important in the care of these vulnerable patients. Nonetheless, nephrologists should understand the background, history, and methods used in determining dialysis dosing based on the dynamics of urea.

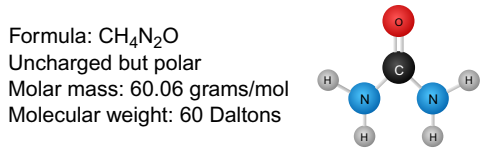
Modeling of any system is an attempt to better understand complex processes by using mathematical approximations. This chapter focuses on urea kinetic modeling (UKM) in determining the dose of HD in adults. We will discuss why urea has been the molecule of choice, describe the modeling techniques in nontechnical terms, outline some simplified equations to approximate the results of UKM, and give some practical troubleshooting tips. For those interested in computer programming or a practical online tool to explore the possibilities of UKM, we include additional references at the end of this chapter.

Why Model Urea?

In stages of chronic kidney disease not requiring dialysis, serum creatinine concentrations are used to estimate kidney glomerular filtration rate. Since the generation of creatinine, which roughly correlates with muscle mass, is relatively constant over time and minimally influenced by dietary variations, it serves well in this role. In measuring HD clearance, creatinine could also conceivably be used as a representative molecule. However, since a reliable method for determining muscle mass and hence creatinine generation rate is not readily available, we shift away from using creatinine as a marker for monitoring HD adequacy. Urea instead was chosen as the marker for HD adequacy as its generation rate is easier to assess (Fig. 4.1). Urea is also inexpensively and readily measured in most clinical laboratories by way of blood urea nitrogen (BUN).

Nitrogen-containing waste products, derived from amino acid breakdown in protein catabolism, are excreted almost exclusively by the kidneys. In humans, nitrogenous waste comes mainly in the form of ammonia, urea, creatinine, and uric acid. Ammonia is toxic at higher concentrations. Many animals, especially terrestrial species, spend valuable energy to transform ammonia to urea, a much less toxic compound. Urea is by far the most plentiful of the nitrogen-containing waste molecules primarily produced by the liver via the Krebs ornithine–urea cycle in a zero-order kinetic fashion (its rate of production is not affected by concentration). Even prior to the advent of dialysis, it was observed that limiting protein intake in patients with advanced kidney failure lessened the signs and symptoms of the condition. So, does this imply that urea is the main toxin of renal failure?

It is evident from prior human and animal studies that the toxicity of kidney failure is not due to urea. However, elevation of the blood urea level loosely correlates with the hundreds of other substances that accumulate in advanced kidney failure, leading to the clinical syndrome of uremia. Similarly, while HD removes urea, it is likely the concomitant clearance of a myriad of other retained toxins that leads to patient improvement. Most importantly, large-scale clinical studies on HD dosing have used the fractional removal of urea to help us understand how the dose of HD relates to morbidity and mortality.



• **Fig. 4.1** As renal failure progresses to dialysis, the clearance of urea, as a representative solute, is used in the dosing of extracorporeal treatments including hemodialysis.

In summary, the attributes of an ideal marker for monitoring HD adequacy would likely embody the following characteristics: (1) it would increase in kidney failure, (2) it would correlate with clinical signs and symptoms of the disease, (3) it would be removable by dialysis, (4) it would be easy and reproducibly measurable, and (5) its degree of removal would be associated with important clinical outcomes. While not a perfect marker, urea serves as an easily accessible and reproducible marker for dialysis adequacy.

The Kinetics of Urea

The word "kinetic" has its root in the Greek term for motion. The BUN at any given moment provides minimal information regarding the condition of the HD patient nor the adequacy of dialysis. For example, a low pre-HD BUN may reflect either a patient who has been receiving excellent routine dialysis clearance or a patient who has poor protein intake and this singular value provides no information on the dynamics of urea. Understanding how the concentration of urea changes over time in the context of urea generation and dialysis removal is the value of UKM.

Nephrologists owe much of the understanding of UKM, the concepts and the mathematics behind it, to Gotch and Sargent, as well as to numerous other scientists and investigators who have further defined and refined the concepts. This section will outline the broad concepts, differing methods, assumptions, and required data for UKM.

Balance Between Urea Production and Removal

The urea concentration in serum, most commonly assessed as BUN, is the balance of urea production from protein breakdown and the removal of urea. In patients with kidney failure on HD, serum urea concentration is constantly changing since its removal by HD is an intermittent process. Urea generation rate (G), expressed in units of mass per unit time (g/day or mg/min), for the purpose of UKM, is assumed to be constant both during and between dialysis treatments. Removal of urea (K) is the sum of dialyzer and native kidney clearances (K_D and K_R, respectively). So, the concentration of urea (C) is a function of its generation rate within the body (G), the body water in which urea is distributed (V), and the clearance of urea by K_D and K_R.

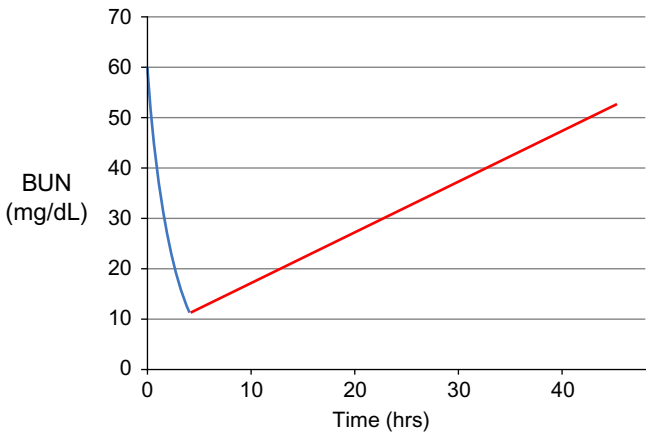
The rate of change in the *amount* of urea (volume × concentration) over time (t) can be written as:

$$\frac{d(V \times C)}{dt} = G - K \times C \qquad (4.1)$$

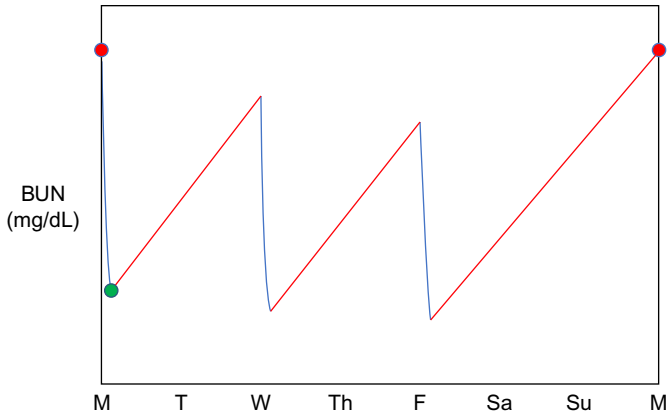
Urea *generation* (G), predominantly by the liver, is a zero-order kinetic process, meaning that its rate of production is not affected by the surrounding concentration. Urea *removal* by dialysis and native kidneys are first-order elimination processes. In other words, the urea removal rate is dependent on its concentration. The rate of urea elimination declines over time for both diffusive and convective clearances since the concentration of the urea in the plasma declines. Therefore, urea concentration in the patient during HD decreases in a logarithmic fashion, and removal becomes less "efficient" over time. Fig. 4.2 illustrates the typical removal and gain of urea. In the process of UKM, two mathematical expressions, one for the rise in urea from generation and the other for the fall of urea from dialysis and any native kidney function, need to be created and solved simultaneously to describe the rise and fall of urea over the course of a week. Fig. 4.3 shows a typical thrice-weekly HD profile for BUN. Note the linear rise in urea between HD treatments (we are assuming no residual kidney function in this example) by zero-order generation of urea, with the curvilinear first-order kinetic decline of BUN during intermittent HD treatments.

Urea Generation and Protein Catabolism

Protein turnover, the balance between anabolism and catabolism, includes the net release of amino acids that are metabolized to urea. Urea production (G) is therefore linked to net protein catabolism. In a steady state, where body protein turnover and dietary protein consumption are constant, the daily production of urea is proportional to dietary protein intake. The generation rate of urea (G in mg/kg/day) has a well-studied relationship to net protein catabolism in the expression:



• **Fig. 4.2** The typical fall and rise of blood urea nitrogen *(BUN)* during hemodialysis (HD) and the following 2 days. First-order elimination kinetics of diffusion and convection, as contributed by HD, would see a logarithmic fall of BUN over the course of HD *(blue line)*. Urea generation, following zero order kinetics, sees the rise in BUN *(red line)* after HD. This example assumes no residual native kidney function.



• **Fig. 4.3** We represent a three times weekly hemodialysis (HD) patient on a Monday, Wednesday, and Friday schedule, with no residual native kidney function. Urea removal by HD *(blue line)* rapidly reduces blood urea nitrogen *(BUN)*. Urea kinetic modeling assumes a constant rate of urea production (*red lines*) over the week, so that the rise in urea over the long intradialytic period brings the BUN level back to where it was pre-HD at the beginning of the week.

$$nPCR = 5420 \times \frac{G}{V} + 0.17, \tag{4.2}$$

where V is total body water volume (the volume of distribution of urea in mL) and $nPCR$ (mg/kg/day) is the net protein catabolic rate that is normalized for lean body weight and body size. The constant of 0.17 represents the stable daily generation of non-urea nitrogen compounds such as uric acid and creatinine. Therefore, when UKM determines a value for G, we get information about nPCR that can be clinically useful in assessing the nutritional status of HD patients.

Urea Removal

Conventional HD relies on diffusion for removal of most uremic toxins. Urea, as the representative uremic substance, is removed primarily by its concentration gradient between plasma and dialysate. Mathematically, this can be delineated by the following:

$$C = C_0 e^{-kt}, \tag{4.3}$$

where C is the urea concentration, C_0 is the initial urea concentration, k is a rate constant, and t is time. If we take Eq. 4.3 and rearrange it by dividing both sides by C_0, taking the natural log (ln), dividing by -t, and then inverting C/C_0 to deal with the negative sign, we get

$$k = \frac{\ln\left(\frac{C_0}{C}\right)}{t}. \tag{4.4}$$

If we then use $k = K/V$, where K is the clearance and V is the urea distribution volume and substitute into Eq. 4.4, we get the familiar term:

$$\frac{Kt}{V} = \ln\left(\frac{C_0}{C}\right) \tag{4.5}$$

If C_0 and C are the pre- and post-HD BUNs, respectively, one notes that it is the ratio or fractional urea clearance and not the absolute values of BUN, which dictates HD treatment adequacy. We also realize our term for fractional urea clearance is unitless. A Kt/V of 1 suggests clearance of the entire water volume. Because HD is a recirculating process, Kt/V can be larger than 1.

The process of modeling the dynamics of urea requires us to make important assumptions and decisions on the degree of complexity of the model. Three common considerations for UKM are discussed in more detail in the next section: (1) the number of water compartments of urea, (2) urea clearance from convective clearance during ultrafiltration, and (3) the effect of residual native kidney function on UKM results.

Modeling Parameters

When the mathematical expressions used in UKM are derived, we need to understand what basic assumptions are being made. Three key assumptions or modeling parameters deserve mentioning. First, we know that there are multiple body water compartments or "pools" in which urea resides. In a steady state, it is assumed that urea is freely distributed throughout these compartments. With the rapid clearance of urea provided by HD, the urea concentration in the vascular water compartment is quickly lowered, and urea in other water compartments needs time to equilibrate across various cell membranes. During HD, urea behaves as being partitioned in these nonvascular water compartments. We can construct urea kinetic models based on envisioning urea distribution in a single compartment or to model it as if it were in multiple compartments, perhaps more accurate to real physiology but adding significant complexity. Second, plasma water removal on HD during ultrafiltration convectively removes small soluble substances. Thus, UKM needs to include fluid removal volume into the mathematical formulas to account for convective urea clearance. And third, residual kidney function, present in a good percentage of

HD patients should ideally be part of UKM, as this can significantly affect the results of modeling, especially on the modeled urea generation rate (*G*).

Single- Versus Multiple-Compartment Models

In normal physiology, urea is considered freely diffusible among the various body water compartments. In normal steady-state physiology, urea distributes total body water as if in a single pool. However, during rapid clearance of urea from the vascular water compartment during HD, a situation not encountered in normal conditions, urea diffusion from other compartments into the vascular compartment encounters membrane resistance. Thus, we can conceptualize and model urea to reside in more than one body water compartment, each with a different partition barrier and intercompartmental mass transfer coefficient (K_C) to the diffusion of urea during HD. Fig. 4.4 graphically represents a single-compartment and a two-compartment model.

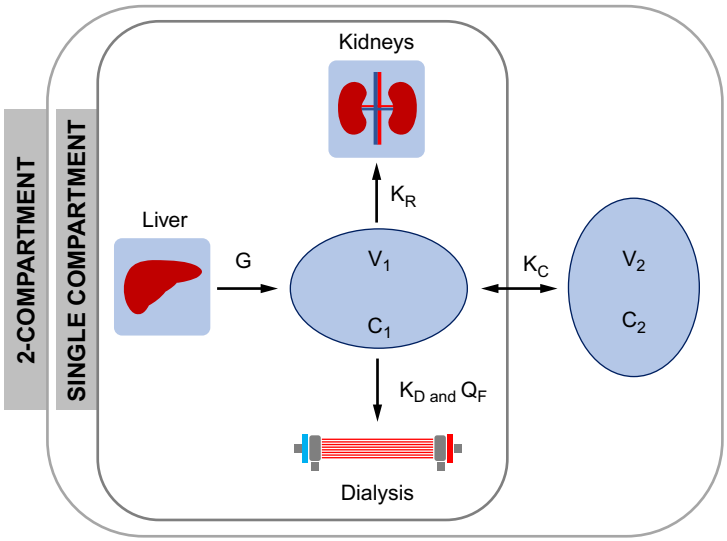
In a multicompartment model, it is assumed that a concentration gradient for BUN develops between the extracellular and intracellular compartments during HD, with the intracellular concentration higher. At the cessation of the treatment, there is continued rise in serum BUN for 30–40 minutes. This diffusion-based "rebound" in BUN is not accounted for in the post-BUN blood test, which is traditionally drawn seconds after the HD blood pump is slowed or stopped.

Multiple-compartment models require additional BUN measures during HD, commonly midway through the treatment, as well as after the rebound phase 30–40 minutes post-termination of dialysis. While these multiple-compartment models may be more representative of actual physiologic changes in BUN during and after HD, the additional work for clinic staff and inconvenience to the patients make multiple-compartment modeling impractical for routine clinical care.

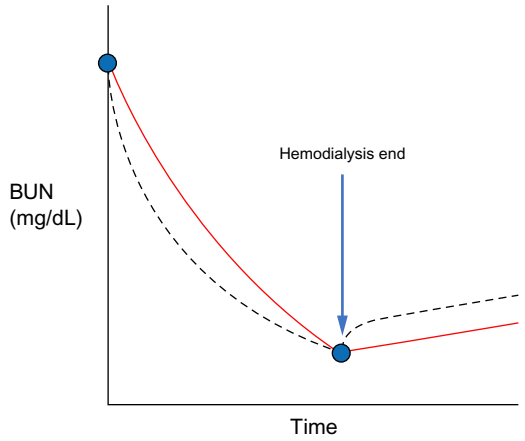
The single-pool or single-compartment model requires only pre- and post-HD BUN values, which fits clinical practice and patient convenience. As it turns out, the single-pool model does a good job of approximating a multicompartment model due to two vital limitations or errors of the single-pool model that must be understood. In a single-pool distribution of urea, there is no accounting for a diffusion barrier to urea during HD, nor a rebound of urea after HD. These two "errors" are illustrated in Fig. 4.5. We know that *V* is the ratio of the *amount* of urea removed on HD to the change in BUN over the course of HD:

$$V = \frac{K_D \times \int_{t=0}^{HD\ duration} Cdt}{\left(C_0 - C_e\right)} \tag{4.6}$$

In Eq. 4.6, *Ce* is the equilibrated post-HD BUN. The numerator is essentially dialyzer clearance K_D multiplied by the area under the curve (AUC) of intradialytic BUN. So, the overestimation of intradialytic BUN AUC in the numerator and the overestimation of the difference between pre- and post-HD BUN in the denominator in the single-pool model are in the same direction and of similar magnitude resulting in off-setting errors. Thus, the single-pool modeled *V* is a good approximation of the modeled *V* from multipool models, and its use in clinical care is justified.



• **Fig. 4.4** Conceptualizing single-compartment and two-compartment models. Urea kinetic modeling considers the generation of urea *(G)* by the liver, residual native kidney clearance of urea (K_R). and removal of urea by dialyzer clearance *(K_D)*. Note that variable volume models would also incorporate hemodialysis (HD) ultrafiltration *(Q_F)* as it alters the water in which urea is distributed and contributes to convective urea clearance. Because of how rapidly HD clears urea from the vascular water space, there is a gradient in concentration of urea *(C_1* and *C_2)* during dialysis between the two water compartments *(V_1* and *V_2)*. The rate of urea movement between various body water pools is represented by the intercompartmental mass area transfer coefficient *(K_C)* in the two-compartment model.



• **Fig. 4.5** The two-compartment model *(dashed lines)* predicts measured intradialytic and posthemodialysis (HD) rebound levels of blood urea nitrogen *(BUN)* accurately. The single-compartment model *(solid red line)* overestimates the interdialytic amount of urea removed based on the area under the concentration curve during dialysis. The single-compartment model does not take into account the rebound that occurs in the 30 minutes post-HD. These two shortcomings of the single-pool model offset each other, and the resulting modeled V is close to that obtained from the two-compartment model.

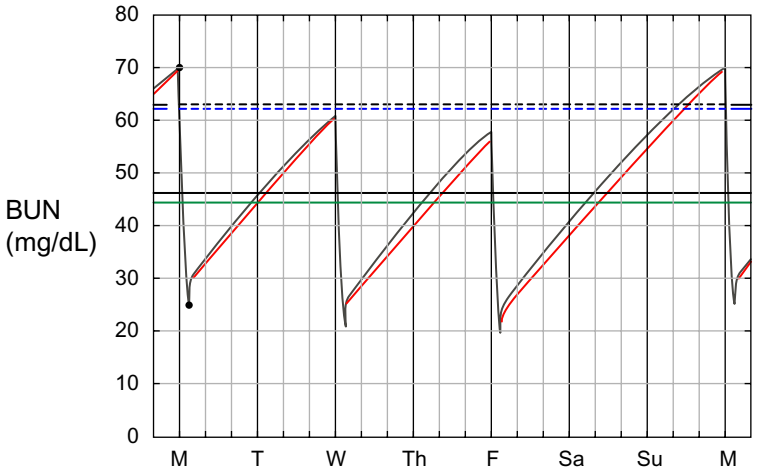
Variable Volume Model

Most dialysis patients gain fluid volume between HD treatments, requiring ultrafiltration to achieve their theoretical dry weight. Plasma water removal provides convective clearance of urea and other substances. The relative contribution of convective clearance should not be underestimated. It is important to understand that this convective clearance will not be represented in the use of some simplified equations such as the urea reduction ratio (URR). For example, in a 70-kg patient with an interdialytic weight gain of 4 L (thus 4 L of ultrafiltration), the convective clearance alone contributes roughly 0.15–0.20 Kt/V to the clearance during that HD treatment. Looking at this another way, modeling Kt/V without accounting for volume removal would significantly underestimate the Kt/V. If one used only URR, the clearance by ultrafiltration would not be included; please see the later section on estimation equations. This also may have implications on the phenomena that patients with higher *V* seem to have lower mortality on dialysis.

Residual Native Kidney Function

Many HD patients, especially in their first incident year of dialysis, still produce urine. This small amount of native kidney urea clearance (K_R), at least based on absolute mL/min, is dwarfed by HD urea clearance. However, K_R is continuous, and HD clearance is intermittent, so K_R can represent a substantial amount of clearance over time. Not including K_R in UKM results in inaccuracies in the estimation of G and the calculation of nPCR.

To illustrate the importance of including residual native kidney function in UKM, take a patient with K_R on three times weekly HD with a pre- and post-HD BUN of 70 and 25 mg/dL, respectively. This patient has a pre- and post-HD weight of 73 and 70 kg. The HD prescription is a time of 180 minutes with blood flow of 400 mL/min, dialysate flow of 600 mL/min through a dialyzer with K_0A of 800. If we include a K_R of 4.0 mL/min in the modeling, *G* is 6.91 mg/min with an nPCR of 1.297 g/kg/day. If we neglect to include the K_R and assume it to be zero, then the modeling gives us a *G* of 4.94 mg/min and an nPCR of 0.973 g/kg/day. Fig. 4.6 graphs the change in BUN over the week for these two scenarios. For the care team, especially the renal dietician interested in the protein intake and nutritional status of the patient, not adding K_R to the modeling will



• **Fig. 4.6** Kinetic modeling results of a theoretical patient on 3 times weekly hemodialysis with and without residual native kidney function (K_R) of 4.0 mL/min. The blood urea nitrogen *(BUN)* modeling line with *(black sawtooth line)* and without *(red sawtooth line)* K_R. We find a difference in time-average concentration of BUN (*horizontal gray line*, without K_R; *green*, with K_R) and in average peak BUN (*dashed horizontal line black*, without K_R; *blue*, with K_R) depending on the inclusion of K_R. We find significantly different modeled urea generation rate (G) and estimated normalized protein catabolic rate if there is K_R; see the text for modeling results. Modeling and graphs performed on Solute-Solver (www.ureakinetics.org).

significantly affect the veracity of the nPCR by greatly underestimating urea generation.

We recommend that residual kidney function be routinely evaluated and formally used in assessing HD adequacy. Using UKM, we can add K_R to HD clearance (K_Dt/V) and report a *total* Kt/V. Since K_R is continuous and K_Dt/V is intermittent, it is not a simple act of mathematical addition. We must inflate the low but continuous K_R into an equivalent intermittent clearance to add it to K_Dt/V. Alternatively, we can deflate K_Dt/V into a continuous clearance equivalent, such as a standard weekly Kt/V (stdKt/V), and then add K_R to it. This will be discussed in the subsequent section on adequacy for alternative HD schedules.

At the present time in the United States, there is unfortunately little incentive to regularly measure and incorporate K_R in HD prescriptions for long-term HD patients. One study found that only about 5% of HD patients had their K_R measured. Regulatory agencies such as the U.S. Centers for Medicare and Medicaid Services require dialysis clinics to report clinical patient measures, including the adequacy of dialysis, most commonly as single-pool Kt/V (spKt/V). At the present time, it is only the dialysis-provided clearance that is reported. Total Kt/V incorporating K_D plus K_R is not a reported measure.

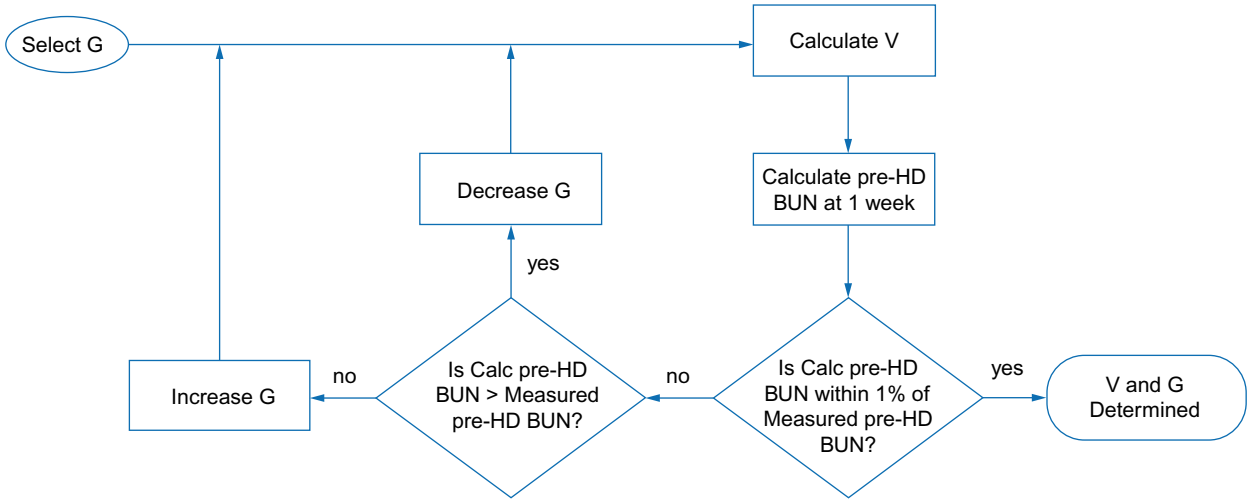
The Process of Urea Kinetic Modeling

Using mathematical expressions to represent both urea generation and urea removal, we can solve and find answers to HD fractional clearance, urea distribution volume, urea generation rate, and nPCR. The equations for HD UKM are beyond the scope of this chapter, but we provide references at the end for readers who are interested.

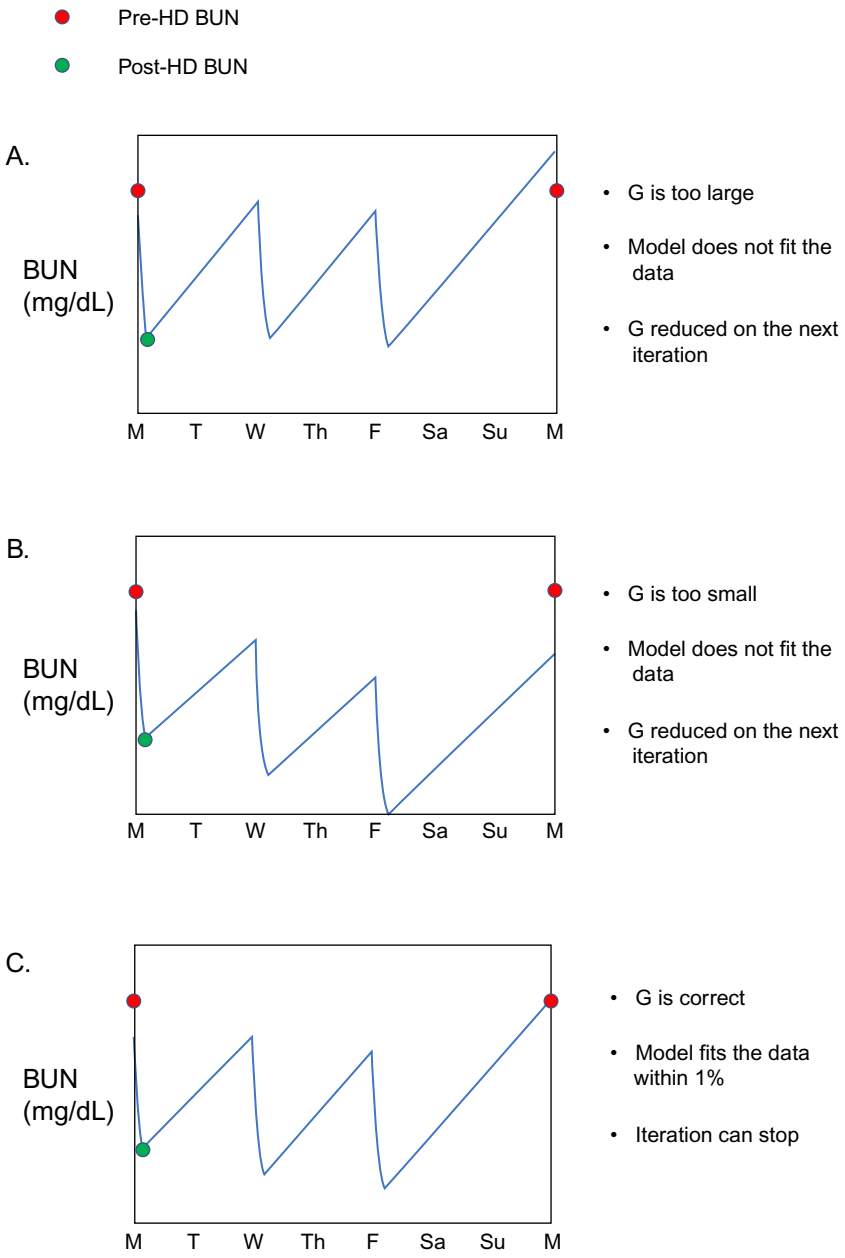
We start the UKM process by obtaining BUN before and after HD. These blood draws, especially the post-HD BUN, need to be done precisely by protocol in order for everything else that follows to be accurate. We mention the potential for modeling errors stemming from BUN lab errors in a later section of this chapter. Using the 2-BUN method of UKM, we can now *fit* these two BUN values into the expressions for urea production and removal to determine *G*, and *V*. Fig. 4.7 gives a flow chart of a typical subroutine that determines *G* and *V* in a 2-BUN modeling method. The modeling program fits the given data in an *iterative* fashion until all parameters are satisfied (Fig. 4.8). These iterations involve trial and error until all factors in this relationship come within some degree of prespecified accuracy, usually within 1%, to the pre- and post-HD BUN values obtained for that HD treatment. This is prohibitively difficult to do manually, and not until the advent of the present-day computer could UKM be implemented on a wider scale. Now, large volumes of information can be entered with results returned in seconds. Once values for *G* and *V* are solved, we can apply what we know about the HD treatment—the dialyzer mass area transfer coefficient (K_OA), duration of HD, ultrafiltration volume, weight, blood, and dialysate flow rates—to get Kt/V. The minimal input data required for kinetic modeling are outlined in Table 4.1.

Studies Assessing Dialysis Adequacy

In 1981, the National Cooperative Dialysis Study (NCDS) was the first U.S. National Institutes of Health (NIH)–sponsored study looking at outcomes based on dose of dialysis as prescribed and monitored by UKM. Treatment groups in this randomized multicenter trial were divided based on long treatment times for groups I and II compared to short



• **Fig. 4.7** Flow chart for determination of V and G by iteration as part of a 2-blood urea nitrogen (BUN) urea kinetic modeling method. In this part of the routine, the computer starts out selecting G, calculates V, determines if the calculated prehemodialysis (pre-HD) BUN is within 1% of the measured BUN. If not, it adjusts G accordingly, and the routine is repeated until the calculated pre-HD BUN "fits" the measured pre-HD BUN. Assumption of a steady state in G is required.



• **Fig. 4.8** The iterative fitting process of urea kinetic modeling. The program chooses a value for G and V and determines if this combination fits the prehemodialysis and posthemodialysis blood urea nitrogen *(BUN)* values. If G is too large **(A)**, the program reruns it with a lower value. If G is too small **(B)**, it uses a larger value the next iteration. In many models, when the error is < 1%, the imputed values are considered satisfactory and that loop of the program concludes **(C)**.

treatment times for groups III and IV (Table 4.2). Groups I and III had low BUN, while II and IV had high BUN. The high BUN group had a substantially higher treatment failure rate, defined as hospitalization or uremic symptoms, compared to the low BUN group. Of note, a fifth group was found in the analysis. This fifth group had a low nPCR (g/kg/day) of 0.60–0.80 and a corresponding 75% treatment failure rate. Failure rate in group V was found to be high irrespective of BUN level. The NCDS results seem to indicate that with normal protein intake and catabolism, underdialysis was associated with poor outcomes, while for patients with poor protein intake and dysfunctional protein catabolism, poor outcomes were present and understandably unresponsive to dose of HD.

When we solve UKM for BUN as a function of nPCR at a constant Kt/V, we see BUN increases linearly with urea generation rate or its analog nPCR. Fig. 4.9 superimposes the urea model solutions over the clinical outcomes of NCDS trial. Groups with low treatment failure rates (I, III) have spKt/V ranging from 0.80 to 1.45. Groups with high treatment failure rates (II, IV, V) have spKt/V < 0.80. It can be inferred that the mechanism common to failure in the high-risk group is a low dose of small solute clearance expressed as the fractional clearance of urea or Kt/V. Also

TABLE 4.1 Minimal Input Data Required for 2-BUN, Variable Volume Urea Kinetic Modeling

Pre- and post-HD BUN
K_OA (mass area transfer coefficient for urea) of dialyzer
Blood flow rate
Dialysate flow rate
Duration of dialysis
Pre-HD weight
Post-HD weight
Frequency of HD per week
Schedule of HD (Monday, Wednesday, and Friday, for example)
Day of the week of blood tests (Monday, for example)

BUN, Blood urea nitrogen; *HD*, hemodialysis.

TABLE 4.2 Study Groups of the National Cooperative Dialysis Study (NCDS) by HD Duration and Pre-HD BUN

Group	Duration on Dialysis (hours:minutes)	Predialysis BUN
I (long treatment, high dose)	4:29	71.2
II (long treatment, low dose)	4:31	104.9
III (short treatment, high dose)	3:19	73.1
IV (short treatment, low dose)	3:14	109.1

BUN, Blood urea nitrogen; *HD*, hemodialysis.

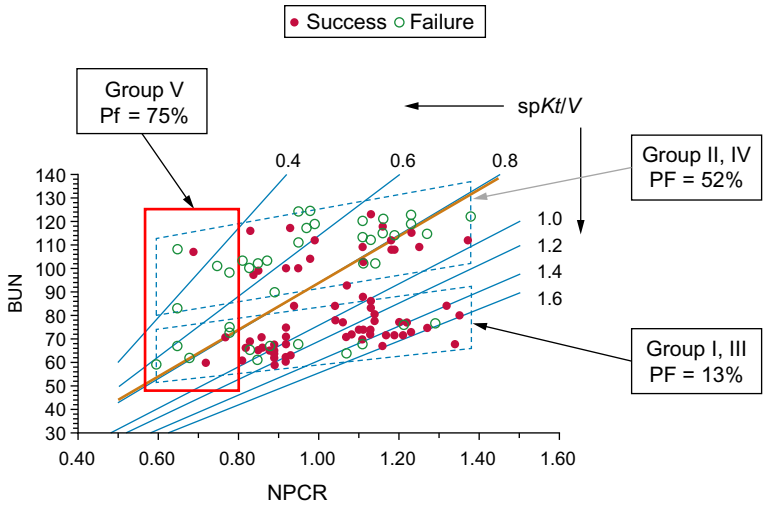
note, that the level of BUN is irrelevant to the definition of adequate dialysis dose. In this way, urea is a generic solute used to model fractional clearance of other low molecular weight toxins. A step function was added to relative risk analysis to construct a modeling line for adequate dialysis. In addition to this, an exponential analysis was also made to assess for a similar modeling line. These two analyses came to differing conclusions. The step function indicated no outcome benefit for spKt/V > 1.00. On the other hand, the exponential analysis indicated increased benefit for spKt/V as high as 2.00.

These differing conclusions of the data resulted in the second NIH-organized randomized controlled trial of HD dose, the HEMO study, in 1994. The initial study design called for a standard-dose arm of spKt/V 1.10–1.20 and a high-dose arm with spKt/V > 1.45. Due to numerous contemporary studies indicating that the minimal adequate ought to be spKt/V > 1.4, the design was changed to targeted doses of 1.40 and 1.75, respectively, in the two arms. The HEMO study definitively showed no improvement in outcome between the two groups. HEMO addressed the high-dose controversy left by NCDS, but it did not address whether there was any improvement in outcomes across a moderate dosage range of 1.0–1.4. Based on the step function applied to NCDS and confirmed by a large pool of retrospective studies, we are confident in declaring spKt/V < 1.0 an inadequate dose of dialysis and associated with poor outcomes. As it is unclear if there is any advantage of spKt/V greater than that and there is no advantage of spKt/V > 1.4, we have focused on minimum adequate dose. Practice guidelines currently recommend a minimum delivered spKt/V of 1.2 over three-weekly HD treatments. The idea behind a recommended dose slightly above the minimum adequate dose is to ensure that no patient gets an inadequate dose. In fact, a prescribed dose of 1.3–1.4 is advised by experts to ensure that no patient receives below the recommended dose.

Studies are still being carried out looking at potential ways to improve the delivery of dialysis. Observational studies have indicated a possible benefit to a frequent dialysis regimen for subsets of patients. The Frequent Hemodialysis Network (FHN) Trial consisted of two randomized controlled trials conducted to assess the benefits of both daily and nocturnal dialysis compared to conventional three times weekly dialysis. In both trials, the power to assess mortality was limited due to low anticipated recruitment, so the primary outcomes were composites of death, change in left ventricular mass index (LVMI), and RAND-36 (RAND Corporation, 36-item survey) quality of life health survey. A number of secondary outcomes were also evaluated in the two trials.

The daily dialysis trial arm compared short daily dialysis sessions (six times a week, 1.5–2.75 hours per session) to conventional three times weekly dialysis (2.5–4-hour sessions). Target Kt/V per session was 0.9 in the daily dialysis group compared to 1.1 in the conventional group. This translated into a delivered Kt/V per week of 3.54 in the daily dialysis group compared to 2.49 in the conventional group. Both groups reached an adequate dose, but there was a significant increase in delivered urea clearance seen in the daily dialysis group. Benefits to both LVMI as well as improved reported RAND-36 scores were seen with daily dialysis.

The nocturnal trial arm compared long nocturnal sessions (three times a week, 6–8 hours per session) to conventional dialysis. Targeted Kt/V per session for the nocturnal group was 1.87 compared to 1.48 for the conventional group. This resulted in a delivered Kt/V of 5.03 in the nocturnal group, which was substantially higher than the 2.91 delivered per week in the conventional group. A positive signal was seen for reduced LVMI, but the nocturnal trial's small sample size made it statistically insignificant. Interestingly, enough patients in the nocturnal group needed significantly less ultrafiltration per session. It was also found that higher



• **Fig. 4.9** National Dialysis Cooperative Trial results by prehemodialysis (HD) blood urea nitrogen (*BUN*), normalized protein catabolic rate (*NPCR*) with HD dosing by single-pool Kt/V superimposed. Percent failure of HD (*PF*) was higher in those with the lowest Kt/V regardless of BUN (groups II and IV), but highest in those with poor nutritional status based on low NPCR, regardless of Kt/V (group V).

calcium and potassium baths were needed for the nocturnal cohort. This improved small molecule clearance occurred with significantly lower blood flows and dialysate flows than in the conventional dialysis cohort. The nocturnal study had a significant cohort of patients with residual renal function, while the daily dialysis trial excluded patients with urea clearance > 3 cc/min. The nocturnal trial showed a clear association of accelerated loss of residual function with nocturnal dialysis compared to conventional dialysis.

The two FHN trials showed benefits for controlling a patient's blood pressure and serum phosphorus with both nocturnal and daily dialysis. Anemia and nutrition status were largely unaffected by dialysis strategy. There was an association of increased vascular access complications in the frequent dialysis groups. The conclusions from the frequent HD network trials are varied and do not definitively answer the role of more frequent dialysis. However, the trial does seem to indicate that frequent dialysis can be done safely. Both daily and nocturnal dialysis delivered a significantly higher dose of dialysis as seen by the delivered weekly Kt/V. In addition, there do seem to be some clear benefits of more frequent treatments, including improved BP management, serum phosphorus control, and prevention of increase of LVMI. Could there be a connection between the higher delivered Kt/V and the improvement with these outcomes in the patients of the trial? That was not answered by the FHN trials. It is clear, however, that frequent dialysis strategies can be administered safely. It is up to nephrologists to apply the possible advantages of alternate dialysis strategies to the individual patient on a case-by-case basis.

Estimation or Simplified Equations

UKM can now be done more easily with the ubiquitous availability of computers. Mathematical equations are also available to approximate the results of formal UKM. These simplified equations require some of the same input parameters as UKM. Handheld calculators or calculator functions on mobile devices suffice in most instances, making results of HD adequacy more quickly accessible in moments when UKM is not available.

The URR is a frequently touted quick-to-use equation:

$$URR(\%) = 100 \times \left(1 - \frac{[PostBUN]}{[PreBUN]}\right) \tag{4.7}$$

A URR of 65%–70% loosely correlates to a single pool Kt/V of 1.2. However, the precision and accuracy of URR are not adequate for long-term, routine monitoring of HD patients. A better estimation equation by Keshaviah uses the natural log function to estimate the nonlinear decline in BUN over the course of HD and still only requires pre- and post-BUN values:

$$Keshaviah\ Kt/V = 1.162 \times \ln\left(\frac{[PreBUN]}{[PostBUN]}\right) \tag{4.8}$$

Neither Eq. 4.7 nor Eq. 4.8 considers the added removal of urea by ultrafiltration or residual kidney function. Expert guidelines, such as those published by the National Kidney Foundation in their Kidney Disease Outcomes Quality Initiative (KDOQI) documents, suggest the use of more sophisticated estimation equations if formal UKM is not used, in routine clinical care.

More accurate equations derived by Daugirdas correlate well with UKM results for three times weekly HD. While requiring more input variables, these simplified equations are acceptable methods for HD adequacy monitoring when formal UKM is not available. The first generation of the equation appeared to overestimate Kt/V at higher ranges.

A second generation of the Daugirdas equation was developed to reduce this overestimation:

$$Daugirdas\ II\ \frac{Kt}{V} = -\ln\left(R - (0.008 \times t)\right) + \left(4 - (3.5 \times R)\right) \times \frac{UF}{PostWt} \quad (4.9)$$

where R is [post BUN]/[pre BUN], t is duration of HD in hours, UF is volume of ultrafiltration in liters, and $PostWt$ is patient weight after HD in kilograms. We want to emphasize that Eq. 4.9 applies to the traditional thrice-weekly HD schedule. For those dialyzing twice or 4-times weekly, see the next section on HD adequacy assessment for non-traditional dialysis schedules.

Hemodialysis Adequacy for Alternative Dialysis Schedules

Not all HD patients may be on a three times weekly treatment regimen. Many patients require four times a week HD, most often in situations where interdialytic fluid gains require an extra weekly HD to avoid symptomatic volume overload. Occasionally, a patient with substantial residual native kidney function may only need two times weekly HD. We can use UKM to determine the per HD fractional urea clearance for schedules other than three times weekly. However, how do we know if the spKt/V is "adequate" for that patient on these alternative schedules? For example, does an spKt/V of 0.8 per HD, four times weekly, provide enough clearance in a patient without K_R? Does an spKt/V of 1.4, twice a week, provide enough clearance if the patient has a K_R of 4 mL/min?

UKM can provide the dialysis Kt/V results for all of these schedules. However, the per-HD target Kt/V will not be that of a traditional thrice-weekly schedule. To deal with these alternative dialysis schedules, we can determine the amount of clearance obtained in a week by using the standard weekly Kt/V (stdKt/V), a concept first proposed by Gotch. This method allows comparisons across different HD frequencies, allows the addition of K_R, and even allows comparison with other dialysis modalities like peritoneal dialysis. Because the Kt/V value determined by UKM or estimation equations is an intermittent fractional clearance of urea during HD, we cannot simply multiply the Kt/V by the number of treatments a week to get stdKt/V. Recall that clearance by diffusion (or convection) becomes less efficient over time, so three times weekly HD for 4 hours per treatment does not give one the same weekly clearance as four times weekly HD for 3 hours per treatment, even though weekly treatment time is 12 hours in both cases. Ideally, we use UKM to get the stdKt/V in these nontraditional HD schedules.

We can also use simplified equations that allow us to approximate the UKM stdKt/V. Eq. 4.10 is a recently modified version of the original stdKt/V—which had been developed for estimating a single-pool, fixed-volume model—that now includes provisions for volume removal, variable frequency per week of HD, and K_R:

$$stdKt/V = \frac{\left(\dfrac{10080 \times \dfrac{1 - e^{-eKt/V}}{t}}{\dfrac{1 - e^{-eKt/V}}{eKt/V} + \dfrac{10080}{F \times t} - 1}\right)}{\left(1 - \dfrac{0.74}{F} \times \dfrac{UF_w}{V}\right)} + \left(K_R \times \frac{10080}{V}\right) \quad (4.10)$$

where eKt/V is the equilibrated Kt/V, t is HD time in minutes, F is the number of HD sessions per week, and UFw is the volume removed on HD for the week. The eKt/V can be approximated by the modified Tattersall equation with a time constant of 30.7, where t is treatment duration in minutes:

$$eKt/V = spKt/V \times \left(\frac{t}{t + 30.7}\right) \quad (4.11)$$

A delivered stdKt/V of 2.1 is desired in HD patients based on expert panel guidelines.

Recognizing Errors

The output performance of any model is only as good as the input data. The monthly Kt/V by UKM should always be interpreted in the appropriate clinical context, and any surprising value should prompt the nephrologist to troubleshoot. For example, if a patient has a Kt/V that is uncharacteristically low or too high to be true, clinicians should be suspicious of an error in the data used in its modeling. Table 4.1 outlines some of the minimal input information used in UKM, and any error in these inputs may affect the results. In using UKM, the clinician should also suspect an error when the modeled V is atypical for the patient, as an individual's V should not deviate dramatically from month to month.

An inappropriate post-BUN is a common culprit for modeling error since the timing of its sampling needs to be done fastidiously. If the post-BUN is drawn too early after blood pump speed reduction, one gets too low of a BUN due to local recirculation. If drawn too late, one gets too high of a BUN due to rebound. Because post-BUN is a lower value than pre-BUN, any absolute inaccuracy translates to a large percentage error.

Other common pitfalls of UKM include inaccurate assumptions for entered values of blood flow and dialysis duration. For example, a patient uses the restroom mid-HD and misses 20 minutes of the prescribed treatment time. The post-HD BUN will be higher with less actual time on HD. If the UKM treatment duration is based on either the prescribed dialysis time or the HD start and stop clock times, the actual time on HD may be lower than what the model presumes. Another example would be a patient who has a problematic arteriovenous shunt or catheter characterized by a high inflow resistance (arterial dynamic pressures

running very negative) throughout the HD. While the blood pump may indicate a blood flow of 400 mL/min (which would be the input into the computer for UKM), the actual delivered blood flow would be substantially lower than that since the roller pump segment does not fully reexpand with each "stroke" of the roller. In this scenario, there would be a lower actual blood flow and hence lower delivered clearance, but the model does not know this. In both of these cases, the model assumes veracity of the input values, the post-BUN would be higher, and a larger than actual V will be modeled.

Conclusion

Nephrologists may not need to know all of the intricacies of formal UKM, but we should understand the concepts underlying this process, the use of simplified equations that estimate UKM reasonably well, and the potential scenarios for output errors. The adequacy of HD, as it pertains to small-molecule clearance, remains most well defined by UKM and the key clinical studies demonstrating the thresholds of Kt/V that now serve as the minimal dose of HD.

Recommended Reading

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5

The Dialysis Prescription

STEVEN BRUNELLI, MD, MSCE

Perhaps the most fundamental prescriptive question is *how much dialysis is enough?* On the surface, this question seems simple. However, this veneer of simplicity is misleading and belies myriad complexities and nuances. The question's apparent simplicity stems from its bounded nature: on the low end, zero dialysis is insufficient and leads to death; on the high end, there exists a finite number of hours per week during which a patient can dialyze; the optimal amount of dialysis must lie somewhere between these two. However, in pinpointing the location of this "optimum," one must confront a series of difficult questions. *(1) What are the direct objectives of dialysis? (2) How does one incorporate patient preferences? (3) Is there a threshold of "enough," or are relationships continuous? (4) How are these answers impacted by temporal changes in sentiment and available technologies?*

Question 1 is philosophical in nature. It is unclear if a consensus answer exists among stakeholders. In fact, the question itself may be too is simplistic in that it does not account for the need to potentially tradeoff among objectives (e.g., maximizing survival versus creating the least burden on quality of life). Question 2 extends uncertainty further. If there be an answer to the first question, that answer exists at the level of the "population" and does not imply conformity or like-mindedness among all patients. Both questions 1 and 2 assume a threshold effect: that there is an amount of dialysis below which outcomes are uniformly bad and above which outcomes are uniformly good. However, question 3 reminds us that the effect of dialysis on the body need not observe a threshold effect, and the relationship may be more incremental. Ergo, the right question may not be "how much is enough?" but rather "when is enough enough?." Finally, question 4 reminds us that whatever the correct answer is—assuming there is a correct answer at a particular time in a particular context—may evolve and change over time.

Perhaps because these issues are so complex and interdependent, research and practice in dialysis have found a need to invoke simplifying paradigms and ask more directive, research-ready questions with empiric answers. In this chapter, we will explore how this line of reasoning has evolved, what it implies for contemporary practice, and how it may change in the future. However, be reminded that even this—the best available line of empiric data and data-driven practice—is by nature a shadow on the wall of Plato's cave, and the reader is encouraged to harken back to earlier, more fundamental questions which may not have objective answers but nonetheless point to truth.

Philosophy of Dialysis Adequacy

Science is quantitative, and clinical medicine, at least semi-quantitative. Therefore, in determining how much dialysis is enough, one must define the means by which dialysis can be quantified. The National Cooperative Dialysis Study was the first rigorous attempt to do so. The trial was begun in the mid-1970s at a time where dialysis had recently become "universally" available in the United States and where recent technological advances had made possible more efficient delivery of dialysis. At this time, there was no systematic tracking of patient survival (the abysmal survival rates among dialysis patients would not be fully recognized until the late 1980s), but providers recognized that many patients continued to feel uremic despite treatment adherence. In this setting, the obvious question was: how does one provide dialysis to patients in order that they not be uremic—the latter operationally defined based on terminal withdrawal from dialysis or hospitalization events? Investigators considered two metrics of dialysis dose: time-average blood urea concentration (50 vs 100 mg/dL) and time on dialysis (2.5–3.5 vs 4.5–5 hours) and randomized patients accordingly using a 2×2 factorial design. The former metric was meant as an index of small molecular weight toxemia and the latter as a proxy for a host of other factors. Upon trial termination, time-average blood urea was clearly associated with patient outcomes, whereas time on dialysis did not bear statistical significance. With the benefit of hindsight, one may question whether a p value of 0.056 in the context of a trial that was stopped early and never met target enrollment was truly indicative of "no association." Nevertheless, it was clear that lower time-average blood urea nitrogen (BUN) led to preferable outcomes. In addition, a urea-based metric benefitted from other obvious advantages: (1) it corresponded to a decade-long legacy of basic uremia research that had used urea as a marker, (2) it was readily measurable, and (3) a single unified measure of dialysis adequacy was more readily

implementable than one that considered multiple domains (i.e., urea *and* treatment time). On this basis, small molecular weight solutes in general and urea, in particular, became the currency by which dialysis adequacy came to be measured, a legacy that persists through the present day.

Kt/V

Leveraging data from the National Cooperative Dialysis Study, Gotch and Sargent introduced the concept of Kt/V in 1985. Kt/V is the mathematical relationship between the rate of urea removal (K) times treatment duration (t) divided by the volume of distribution for urea (V). Kt/V was, in essence, part of the emerging urea-centric tradition but broke from the existing paradigm in two key respects. The first distinction was that Kt/V attempted to balance urea removal (the numerator, K*t) to physiologic need (the denominator, V). The second distinction is subtle but nonetheless important: it changed the paradigm by which urea was considered from *how much is there in the body?* to *how much is removed during dialysis?* In typical mid-1980s circumstances, this distinction would have been academic: technologies were reasonably homogenous, and nearly all hemodialysis patients were dialyzed according to a thrice-weekly hemodialysis schedule. However, as we shall see later, interim changes in dialyzer efficiency and greater use of quotidian hemodialysis regimens have necessitated subsequent adaptations.

To be technically precise, Gotch and Sargent's original concept of Kt/V has subsequently been dubbed single-pool Kt/V (spKt/V). This name derives from the conceptual kinetic model through which the equations were derived, which are largely analogous to first-order elimination kinetics. Within the original paper, and more so subsequently in later papers, there are a number of mathematic equations by which spKt/V can be calculated. Perhaps the most popular of these is the Daugirdas formula, which states:

$$\text{spKt/V} = -\log\left(\text{R} - 0.03\right) + \left[\left(4 - \left(3.5^{*}\text{R}\right)\right) \times \left(\begin{matrix}\text{Ultrafiltration volume/}\\ \text{body weight}\end{matrix}\right)\right],$$

where R is the ratio of postdialysis to predialysis BUN.

The use of closed-form equations to calculate Kt/V has been largely supplanted by iterative computer algorithms—the most popular of which is termed "urea kinetic modeling"—the Daugirdas equation is nonetheless revealing as to the constituent components of spKt/V. The first term in the equation (quantitatively the most important) describes the amount of urea that is removed from the start to the end of a dialysis treatment; this is an alternative mathematical formulation of the urea reduction ratio (URR), which will be discussed in the next section.

The second term in the equation corrects for urea generation during the dialysis treatment itself. To understand this term, consider that the typical thrice-weekly in-center hemodialysis patient spends approximately 7% of the time (12 of 168 hours) on dialysis; therefore, one would anticipate that at least 7% of urea is generated during dialysis itself (perhaps more if one considers the catabolic nature of hemodialysis). The effect of this is that the change in body urea content will underestimate the amount of urea being removed, an effect for which this term attempts to compensate.

The third term in the equation accounts for urea that is removed convectively through ultrafiltration. Because urea is freely permeable across the dialysis membrane, it exists in essentially equal concentration in the blood as in ultrafiltrate. Therefore, although urea is removed in the process of ultrafiltration, this is not otherwise reflected in the blood urea concentration.

The latter two terms are necessary because the prevailing paradigm is to measure urea removal on the patient side (i.e., by changes in blood chemistry) rather than on the drain side (i.e., by analysis of spent dialysate). (This is the only practicable solution: it is far easier to collect and analyze 14 mL of blood than 100+ L of spent dialysate.) However, as a thought experiment, consider a counterfactual circumstance where urea removal was assessed drain side: in this circumstance, no correction would be needed for urea generation or convective clearance. Both terms are similar in that they upwardly adjust spKt/V for factors not reflected directly in blood urea concentration change.

Urea Reduction Ratio

URR is a measure of the proportionate reduction in BUN over the course of dialysis. It is calculated as:

$$\text{URR} = 100\% \times \left(\begin{matrix}\text{predialysis}\\ \text{BUN}\end{matrix} - \begin{matrix}\text{postdialysis}\\ \text{BUN}\end{matrix}\right) \Big/ \text{predialysis BUN}$$

It is an alternative expression of the R term in the Daugirdas equation for spKt/V. For example, if a patient started dialysis with a BUN of 100 mg/dL and finished dialysis with a BUN of 30 mg/dL, R would equal 0.3, and URR would equal 70%. As thereby implied, there is an inherent mathematic correlation between URR and spKt/V. Discrepancies between URR and spKt/V derive from three primary sources: (1) URR is not directly indexed to body size, (2) URR does not directly account for urea generation during dialysis, and (3) URR does not account directly for convective urea losses. Nonetheless, the two are largely considered interchangeable, and both are endorsed by guideline committees as valid markers of dialysis adequacy.

Thresholds for spKt/V and URR

In the initial description of spKt/V by Sargent and Gotch, they considered a cutoff spKt/V of 0.9, which best distinguished between treatment failure and success. Recall that success and failure were defined in that study as hospitalization or terminal withdrawal from dialysis.

Beginning in the early 1990s, there was a proliferation of observational studies that looked at the association between achieved urea removal and mortality. Survival was incrementally higher at URR up to 65% and at higher spKt/V up to 1.2. Ultimately, guidelines were issued that espouse spKt/V of 1.4 and/or URR of 70% (buffers added to guard against inadvertent "missed" targets or treatments) indicative of minimally adequate dialysis.

At the time these initial studies were conducted, comparatively few patients had spKt/V much greater than 1.4 or URR much greater than 70%. Therefore, these studies could not assess with precision whether upstream URR or spKt/V may have led to even greater survival advantage. In parallel, technological changes to dialyzers greatly improved the efficiency of urea removal. By the mid-1990s, it had become tenable to achieve greater urea removal in the context of thrice-weekly in-center hemodialysis than had previously been the case. The HEMO Study was launched to explore whether targeting higher Kt/V led to incrementally better survival. Patients were randomized to higher versus lower Kt/V; technically, Kt/V was defined based on equilibrated Kt/V (which will be discussed later) but was functionally equivalent to spKt/V of 1.25 versus 1.65. (Also, the HEMO Study randomized according to high- versus low-flux dialyzers in a factorial design, but that is beyond the scope of this chapter.) The HEMO Study found no survival benefit for higher versus lower Kt/V targets, which served to reinforce existing Kt/V targets.

Equilibrated Kt/V

Use of urea as the currency for small molecular weight dialytic clearance is based on the notion that urea is freely permeable to membranes. Urea is small (molecular weight 60 D) and uncharged, which are ideal characteristics for promoting passive diffusion across lipid bilayers. When one considers the local environment only, indeed, urea is rapidly transferred across cellular membranes ($K_{flux} = 1 \times 10^7$ mmol/cm^2/s) and similarly across dialyzer membranes.

However, in in vivo systems, the picture is more complex. Individual vascular beds are differentially perfused. Urea present in less perfused tissues has less access to the central circulation and, thereby, is less available for dialytic removal. Moreover, there are vascular beds for which perfusion decreases during dialysis (in response to circulatory stimuli and the neuroendocrine milieu). Together, these regions form a reservoir for urea and other otherwise-freely transferrable solutes. In other words, small molecule clearance from these regions is kinetically limited.

spKt/V and typically URR as well are calculated based on urea concentrations measured at the end of the dialysis treatment. These levels reflect well the behavior of urea in the blood at other highly perfused tissues; however, they do not reflect the behavior of urea in more inaccessible tissues. Thereby, spKt/V and URR tend to overestimate total body urea clearance.

In fact, if one serially samples blood urea after the end of dialysis, one observes a "rebound" in blood urea levels that represents the re-equilibration of urea across body fluids. Equilibrated Kt/V (eKt/V) is a metric used to account for the overestimation inherent to spKt/V and is derived by sampling postdialysis blood 30 minutes following dialysis as opposed to immediately at the end of treatment.

eKt/V may be a superior measure of total body clearance of low-molecular-weight solutes. However, there is no empiric evidence to suggest that outcomes are superior when eKt/V—as opposed to spKt/V—is used to gauge dialysis adequacy. Moreover, there are logistical barriers to sampling blood 30 minutes after dialysis, including considerations of shift turnover and patient travel. Perhaps for these reasons, eKt/V has not seen widespread clinical adoption in the United States. Current guidelines do not provide a benchmark level for eKt/V. However, for adherents, it may be possible to convert spKt/V thresholds to eKt/V: eKt/V is typically between 0.15 and 0.25 lower than spKt/V.

Standardized Kt/V

Standardized Kt/V is a concept that has been introduced in an attempt to account for modalities other than thrice-weekly in-center hemodialysis. Consider that peritoneal dialysis is delivered on a continuous or near-continuous basis throughout the week rather than on an episodic basis. Therefore, a paradigm of measuring solute removal on the basis of discrete treatments (as is inherently the case with spKt/V and eKt/V) is not applicable. Likewise, home hemodialysis is often delivered more often than thrice weekly, thereby lessening the solute removal requirements for individual treatments. Standardized Kt/V attempts to account for these factors by considering solute removal over the course of the week rather than for individual treatments. Over time, standardized Kt/V has been retroacted for thrice-weekly in-center Kt/V, and conversion tables are available. However, its application to in-center hemodialysis is most often undertaken in research settings, and it has not become the normative means of assessing in-center hemodialysis adequacy in clinical practice.

The specific recommendations regarding what constitutes an adequate standardized Kt/V are largely based on expert opinion rather than empiric evidence, have shifted over time, vary by modality, and will likely continue to do so. The most recent guidelines from the International Society for Peritoneal Dialysis acknowledge a nominal target standardized Kt/V of 1.7. Reassuringly, the guidelines explicitly recognize the limitations of narrowly focusing on small molecule clearance, or indeed on any single aspect of care, and recommend instead a more holistic assessment of dialysis adequacy that focuses on "maintaining [patients'] clinical well-being, quality of life, ability to meet life goals and at the same time minimize treatment burden."

Middle Molecule Clearance

To this point, we have considered dialysis adequacy only in terms of low-molecular-weight solute clearance or, more accurately, solutes whose kinetic behavior mimics that of urea. In contrast, "middle molecules" are a group of compounds that are biologically relevant but are removed less efficiently by dialysis. The name "middle molecules" harkens to the molecular weight of many such compounds that are middling in nature: falling between that of urea and other compounds readily cleared across dialytic membranes and that of proteins and glycoproteins that are typically too large to dialyze off. However, middle molecules also encompass low-molecular-weight compounds that are inefficiently removed during dialysis due to polyvalence (which limits dialytic membrane flux), protein binding, or intracellular sequestration.

The effects of certain middle molecules such as phosphate and B2-microglobulin have been extensively studied. For these, it is clear that accumulation is pathogenic. Emerging evidence suggests that metabolic byproducts such as p-cresol sulfate, indoxyl sulfate, methylamine, and dimethylamine may be relevant uremic solutes, but these have received comparatively less study. It is clear, however, that despite nearly four decades of research, there is no comprehensive litany of middle molecules. Nor is it certain—and, in reality, it is unlikely—that all middle molecules will behave similarly to one another with respect to dialytic removal. At present, there is no reliable means by which to consider middle molecules into the calculus of dialysis adequacy. Additional research in this area is sorely needed.

Fluid Removal

All too often, canonical dialysis "adequacy" (meaning low molecular weight clearance) and fluid removal are considered in parallel. Textbooks draw the distinction between solute clearance, which is predominantly diffusive in nature, and fluid removal, which is convective. Trainees are typically taught that treatment time is determined by Kt/V considerations and fluid status by specification of target weight.

In a bygone era, this simplistic heuristic was seemingly reasonable. Solute clearance was very inefficient by today's standards, which afforded plenty of time for fluid removal. (In practice, fluid removal did not always go so smoothly, but this was more a consequence of inaccuracies in monitoring ultrafiltration volumes more so than due to implied time constraints.) Over decades, dialyzer technologies have evolved markedly. As a result, urea removal goals could be achieved increasingly more rapidly. This is evidenced by the trend in mean dialysis treatment times in the United States, which fell from 6 hours or more in the early 1970s to 3 hours by the late 1980s.

Greater dialyzer efficiency coupled with a urea-centric paradigm for determining treatment times implies the need for more rapid ultrafiltration during dialysis. Greater ultrafiltration rate portends both labile blood pressure during dialysis and frank intradialytic hypotension, which, in turn, are associated with transient interruptions in end-organ perfusion. Until recently, it was believed that such phenomena were clinically relevant only in as much as they triggered overt clinical events or patient symptoms. However, converging lines of research indicate that the accumulation of subtle insults from subclinical events is of importance. For example, recent work demonstrates that low blood pressure during dialysis (e.g., <90 mm Hg; <100 mm Hg) is associated with increased risk of all-cause and cardiovascular mortality, and in fact, this relationship is not potentiated when only symptomatic episodes are considered. Additional data demonstrate that transient interruptions in perfusion, often asymptomatic in nature, contribute substantively to transient myocardial stunning and white matter damage, which in turn are associated with cardiovascular events and neurocognitive deficits, respectively.

Viewed in this light, it is not surprising that more rapid ultrafiltration is associated with a greater risk of mortality, particularly cardiovascular mortality. In theory, such observations could be confounded because greater interdialytic weight gain both implies more rapid ultrafiltration and independently associates with poor prognosis. However, matched pair analysis indicates that even if patients are exactly matched on interdialytic weight gain (and body weight), those with the higher ultrafiltration rate (i.e., those with lower treatment time) have a higher adjusted risk of death.

Importantly, ultrafiltration rate is defined as volume removed per unit time per kilogram of body weight. Associations between absolute ultrafiltration rate, defined as volume removed per unit time—not indexed to body weight—is less potently associated with clinical outcomes (unpublished observation). In essence then, the relevant parameter related to how rapidly fluid is being removed relative to total body water (perhaps more accurately to extracellular volume, although dedicated studies in this regard have not been conducted). This construct fits well into the framework of interruption of end-organ perfusion. As well, this may partially underlie the body-weight paradox of dialysis whereby smaller patients consistently demonstrate poorer survival than larger patients. Differences in interdialytic weight gain between smaller and larger patients are comparatively less than differences in time needed to achieve spKt/V targets; thereby, smaller patients tend to have higher ultrafiltration rates, on average, than do larger patients.

Best available evidence suggests that risk begins to inflect when ultrafiltration rate crosses 10 mL/h/kg body weight and becomes statistically significantly elevated when in excess of 13 mL/h/kg body weight. Further evidence is needed to confirm (or refute) precise thresholds vis-à-vis safe ultrafiltration rates. In the United States, an ultrafiltration rate >13 mL/h/kg body weight has been adopted by the Centers for Medicare and Medicaid Services as a clinical performance measure, and facilities are graded based on the percent of patients who exceed this threshold.

Of note, ultrafiltration rate has been studied as an average rate for dialysis sessions: net fluid removal divided by total treatment time indexed to body weight. There has been no direct study of whether techniques such as sequential ultrafiltration-hemodialysis or biofeedback technologies modulate associations. Unfortunately, a recently completed clinical trial has shown that ultrafiltration profiling, the technique by which the rate of ultrafiltration is varied over the course of dialysis in an attempt to better match patients' physiology, which previously had been thought to ameliorate hypotension and promote hemodynamic stability, was ineffective in this regard.

The sobering reality is that patients do not want more dialysis, whether in the form of longer or more frequent treatments. In a recent survey, fewer than one-quarter of respondents indicated a willingness to extend treatment time by 30 minutes, and fewer than one-eighth indicated that they would be willing to increase the frequency of dialysis. Clearly, additional patient education is needed to underscore the benefits of mitigating excessive fluid removal rates.

A number of potential adjuvant therapies lurk on the horizon. These include wearable ultrafiltration devices and drugs that block the uptake of sodium from the gut. Although such therapies are unlikely to fundamentally alter the association between ultrafiltration rate and outcome, they hold promise to reduce the net need for ultrafiltration during dialysis, which may enable reduction in treatment times in a safe and tolerable manner. However, rigorous studies are needed to delineate the safety and efficacy of such treatments and to determine how they are incorporated into the fabric of clinical care.

Conclusion

In conclusion, urea kinetics—specifically the achievement of an spKt/V of 1.2 and/or a URR of 65%—are a necessary component of adequate dialysis. Emerging evidence indicates that the prescription should also include a tolerable ultrafiltration rate—optimally less than 10 mL/h/kg but certainly no more than 13 mL/h/kg. Available data do not inform with respect to how best to incorporate middle molecule clearance into the dialysis prescription, but the reader is advised to monitor the literature for advances in this regard. Finally, as in all of clinical medicine, care should be tailored to individual patients based on circumstances and preferences rather than in a cookie-cutter approach.

Recommended Reading

Brown EA, Blake PG, Boudville N, et al. International society for peritoneal dialysis practice recommendations: prescribing high-quality goal-directed peritoneal dialysis. *Peritoneal Dial Int.* 2020;40(3):244–253.

This paper outlines guidelines for the assessment of dialysis adequacy in peritoneal dialysis and the underlying rationale.

Daugirdas JT. Second generation logarithmic estimates of single-pool variable volume Kt/V: an analysis of error. *J Am Soc Nephrol.* 1993;4(5):1205–1213.

This paper described and validates the Daugirdas formula for calculating single-pool Kt/V.

Dobre M, Meyer TW, Hostetter TH. Searching for uremic toxins. *Clin J Am Soc Nephrol.* 2013;8(2):322–327.

This article reviews the candidacy of and biology regarding middle molecules and other solutes that are poorly cleared using conventional dialysis.

Enkoyan G, Beck GJ, Cheung AK, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med.* 2002;247(25):2010–2019.

This is the primary report of the HEMO Study indicating that higher versus standard equilibrated Kt/V does not incrementally impact survival.

Flythe JE, Brunelli SM. The risks of high ultrafiltration rate in chronic hemodialysis: implications for patient care. *Semin Dial.* 2011;24(3):259–265.

This article reviews the evidence linking rapid ultrafiltration to adverse patient outcomes.

Gotch FA, Sargent JA. A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). *Kidney Int.* 1985;28(3):526–534.

This paper introduced the concept of Kt/V based on findings from the National Cooperative Dialysis Study.

Lacson E, Brunelli SM. Hemodialysis treatment time: a fresh perspective. *Clin J Am Soc Nephrol.* 2011;6(10):2522–2530.

This article reviews how considerations of dialysis adequacy evolved over time.

Lowrie EG, Laird NM, Parker TF, et al. Effect of the hemodialysis prescription of patient morbidity: report from the National Cooperative Dialysis Study. *N Engl J Med.* 1981;305(20):1176–1181.

This is the primary repot of the National Cooperative Dialysis study, which showed that lower versus higher time-average blood urea nitrogen was associated with better outcomes.

National Kidney Foundations. KDQOI clinical practice guidelines and clinical practice recommendations for 2006 updates: hemodialysis adequacy, peritoneal dialysis adequacy and vascular access. *Am J Kidney Dis.* 2006;48(suppl 1):S1–S322.

These are the current guidelines regarding minimally adequate dialysis. At this writing, an update to these guidelines is under development. HYPERLINK "file:///C:\Users\sbrunelli\Downloads\UltrafiltrationRateUFR%20(1).pdf"file:///C:/Users/sbrunelli/Downloads/UltrafiltrationRateUFR%20(1).pdf

This document describes the use of ultrafiltration rate as a clinical performance measure.

6

Selecting a Dialyzer: Technical and Clinical Considerations

WILLIAM R. CLARK, MD • CLAUDIO RONCO, MD

Introduction

During hemodialysis (HD), solutes and water are removed through a semipermeable membrane using different separation mechanisms (diffusion, convection, adsorption, and ultrafiltration). The traditional classification scheme for dialysis membranes has been based broadly on composition and water permeability.[1] However, advances in biomaterials and improved fiber production (spinning) technology have led to consideration of several other parameters for membrane characterization, especially new permeability indices.[2]

While the dialysis membrane is the most important determinant of HD performance (i.e., solute clearance), the dialyzer in which it is housed is the device that is actually prescribed by the clinician for treatment. In this chapter, the characteristics of dialyzers used in clinical practice are discussed, with particular attention paid to the parameters that most importantly influence performance. Specifically, the effect of dialyzer design on the mechanisms primarily mediating solute removal, namely, diffusion and convection, is highlighted. While the chapter largely focuses on dialyzer characteristics related to performance, a brief discussion of biocompatibility is also provided. The chapter includes information about newer and emerging applications, with emphasis on therapies designed to remove large molecular weight uremic toxins. The final section summarizes the important considerations for the clinician in selecting a dialyzer.

Hollow Fiber Dialyzers: Fundamental Considerations

The introduction of the hollow fiber artificial kidney revolutionized the field of dialysis in the late 1960s. Relative to its predecessor, the parallel plate dialyzer, the specific advantages of a hollow fiber configuration include an improved surface-to-volume ratio in the blood compartment (shorter diffusion path lengths), along with decreased boundary layer effects and acceptable axial (end-to-end) pressure drops.

With regard to membrane material, dialysis membranes have been categorized traditionally into cellulosic and synthetic groups[3] (Table 6.1). While unmodified cellulosic membranes were used extensively in the past, their utilization has dropped precipitously over the past decades to the current point of effective absence from the market. Although the performance and functional characteristics of some modified cellulosic membranes are similar to those of synthetic membranes, utilization of the former group continues to fall. As such, this chapter largely addresses synthetic membranes.

In preparation for constructing a dialyzer, several thousand (approximately 10,000–17,000) individual hollow fibers are assembled and wound together to form a "bundle" having defined characteristics, including a specific fiber spatial arrangement and packing density[4] (Fig. 6.1). These parameters influence interfiber dialysate flow distribution, an important determinant of dialysate-side mass transfer. After this fiber bundle is inserted into the plastic housing of the dialyzer, additional steps occur, including the application of a polyurethane ("potting") compound at either end of the bundle to encapsulate the fibers, along with sterilization of the finished dialyzer product. Steam sterilization has gained popularity over the years, while the use of ethylene oxide has fallen. Polyurethane can act as a reservoir for ethylene oxide, resulting in the possibility of clinically relevant amounts of residual ethyl oxide in the dialyzer after pretreatment rinsing.

Although not the focus of this chapter, a few basic principles related to biocompatibility are worth highlighting. The traditional parameter for characterization of dialysis membrane biocompatibility has been complement activation, and one of the original driving forces for the introduction of synthetic membranes was attenuation of this phenomenon (relative to unsubstituted cellulosic membranes).[5] However, other indices have been studied, including those related to cytokine activation, effects on inflammatory cells, and coagulation.[1] Moreover, certain principles generally governing the exposure of flowing blood to a biomaterial apply to the

TABLE 6.1 Classification of Dialysis Membranes[a]

	Wall Thickness (μm)	Structure	Flux
Modified cellulosic	6–15	Symmetric	Variable
Cellulose acetate (CA)			
Cellulose triacetate (CTA)			
Synthetic	20–50	Variable	
Polysulfone (PS)		Asymmetric	
Poly(aryl)ethersulfone (PES)		Asymmetric	
Polyacrylonitrile			
Unsulfonated (PAN)		Asymmetric	
Sulfonated (AN69)		Symmetric	
Polymethyl-methacrylate (PMMA)		Symmetric	
Vitamin E-bonded (PS)		Asymmetric	

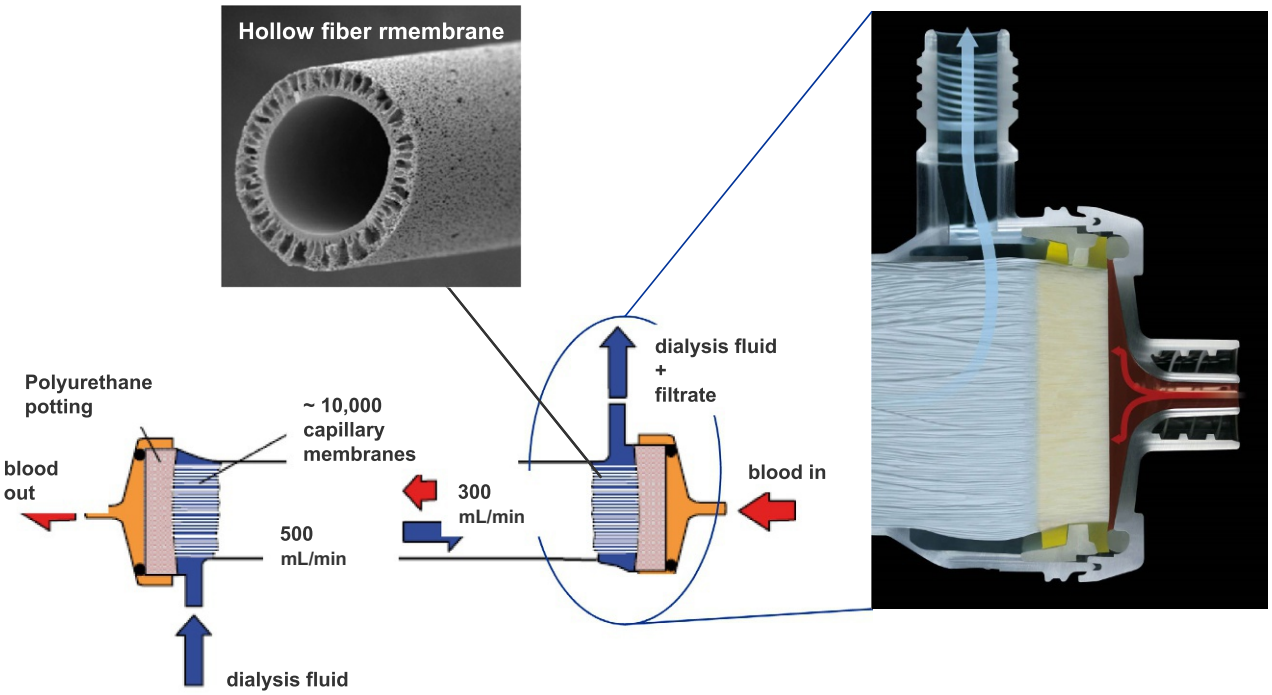
[a] Due to their infrequency of use (almost abandoned), unmodified cellulosic membranes are not included.

case of HD. First, it is well described that both the inflammatory potential, as measured by cytokine and complement activation along with other indices, and the thrombogenic propensity of a biomaterial are mediated by the nature of the layer of proteins adsorbed instantaneously to the membrane surface. (The effect of protein adsorption on membrane performance is discussed later.) From the perspective of thrombogenicity, the biomaterial literature clearly differentiates low-flow conditions, in which clotting is mediated predominantly by the coagulation pathway, from high-flow conditions, in which shear-induced platelet effects assume an important role.[6] Although not clearly elucidated, both of these phenomena probably influence the thrombogenic potential of a particular dialyzer. Finally, it should be emphasized that the biocompatibility of a treatment is a function of not only the dialyzer but also the entire dialysis system, including the blood tubing and all other biomaterials in the extracorporeal circuit along with the fluid to which the patient is exposed.

Hollow Fiber Membrane Characteristics

Influencing Dialyzer Performance

Based on the spinning process used in the manufacture of hollow fiber membranes for HD, it is impossible to produce a membrane with uniform pore sizes. Nevertheless, one of the major goals of the manufacturing process is to produce a membrane with a relatively narrow distribution of pore



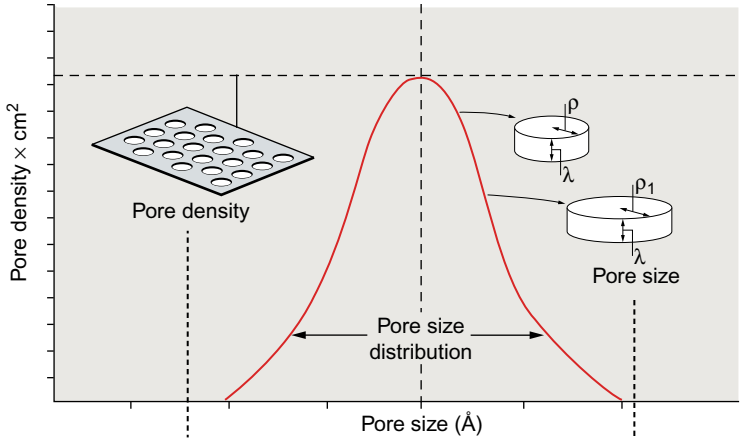
• **Fig. 6.1** Components and Operational Characteristics of a Hollow Fiber Dialyzer.

sizes around a desired average pore diameter that, in turn, determines the overall solute and water permeability properties[3] (Fig. 6.2). In general, a tight pore size distribution corresponds to a relatively sharp molecular weight cutoff for solute depuration, providing a demarcation between large molecular weight uremic toxin removal and albumin loss for high-flux dialyzers.

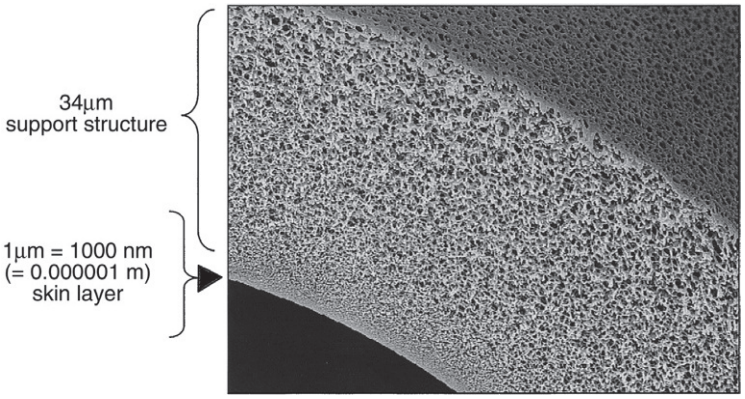
From a structural perspective, the wall thickness values for contemporary synthetic membranes generally range from 20 to 50 μm. However, the majority of synthetic membranes used for contemporary HD have an asymmetric structure in which a thin inner "skin" layer (approximately 1 μm or less) at the membrane–blood interface serves as the primary size-discriminating element with respect to solute removal.[3] The remaining wall thickness ("stroma") acts as a support structure that also provides substantial surface area for molecules that are removed by adsorption. As opposed to the compact nature of the skin layer, the structure of this component of the membrane is relatively open (Fig. 6.3).

In HD, the flow of blood tangential to the membrane surface helps create concentration gradients for diffusive solute removal. Hollow fibers typically have an inner (blood compartment) diameter of approximately 180–220 μm and length of 20–24 cm, resulting in membrane surface areas generally in the 1.5 to 2.5 m^2 for most contemporary dialyzers.[7] The major incentive for reducing hollow fiber inner diameter is enhanced diffusive mass transfer due to reduced diffusion path length within the blood compartment. Moreover, the inverse proportionality between channel width and shear rates (at constant flow rates) leads to attenuated blood-side boundary layer effects for smaller diameters.[8] However, there are limits on the extent to which a reduction in inner diameter can be achieved practically[3] due to the resultant increase in flow resistance. When this occurs, a proportional increase in the axial (arterial to venous) pressure drop is required to achieve a specific blood flow rate. In fact, flow resistance is related to the inverse of the fourth power of the hollow fiber inner diameter—as such, a small change in diameter results in a large increase in resistance.

Hydraulic flux (water permeability) has been the most common criterion used traditionally to classify dialysis



• **Fig. 6.2** Relationship Between Pore Size Distribution and Pore Density. These parameters also influence diffusive permeability, expressed as the mass transfer coefficient-area product (KoA), along with membrane sieving properties.



• **Fig. 6.3** Characteristics of an Asymmetric Polysulfone Membrane. The inner skin dictates the depuration properties of the membrane while the remainder of the wall provides mechanical support and surface area for adsorption of larger molecular weight substances.

membranes.[1] The clinical parameter used to quantify water permeability, Kuf (mL/h/mm Hg), is derived from the relationship between ultrafiltration rate (Qf) and transmembrane pressure (TMP) over a clinically relevant range of the latter parameter. The rate of ultrafiltrate flow through membrane pores is roughly proportional to the fourth power of the mean pore radius (i.e., r^4) of the membrane at constant TMP. As such, the membrane parameter having the most significant influence on water flux is the average pore size. While the water permeability of a dialyzer is a specific property characterizing a "clean" (i.e., unfouled) membrane, its effective value is dynamically influenced by protein/membrane interactions during the course of a typical treatment, as discussed later.

Diffusive Solute Transport During Hemodialysis

Consideration of Each Dialyzer Component

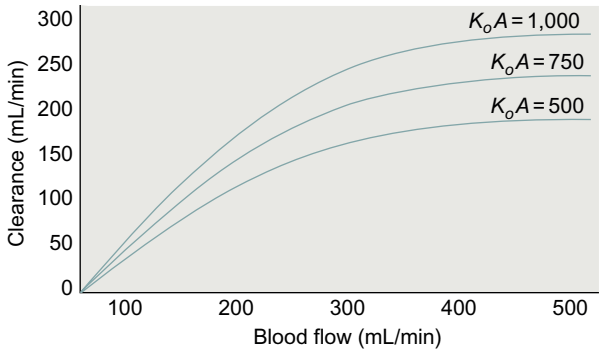
Diffusive mass transfer in a dialyzer is typically expressed in terms of the overall resistance to mass transfer (R_O) and the overall mass transfer coefficient (K_O). (Please note that the latter term should not be confused with clearance.) Overall mass transfer resistance accounts for the three major components of the dialyzer[9]:

$$R_O = R_B + R_M + R_D \quad (6.1)$$

where R_B, R_M, and R_D are resistances contributed by the blood compartment, membrane, and dialysate compartment, respectively. As these three parameters can be viewed as resistances in series, the overall resistance to mass transfer for a particular solute has a "controlling" component, which identifies the dialyzer aspect contributing most significantly.

While blood compartment resistance typically is controlling for small solutes (irrespective of dialyzer type), membrane resistance becomes most important at a certain molecular weight, with the transition occurring at lower molecular weight for low-flux dialyzers due to relatively small mean pore sizes. However, even though the membranes of high-flux dialyzers have more open pore structures, the controlling resistance becomes the membrane itself relatively rapidly in this case also, as solute molecular weight increases. In general, this is the case for solutes having molecular weights greater than 500 Da. As suggested earlier, blood flow rate and hollow-fiber diameter (diffusion path length) are the two most important determinants of resistance to small solute mass transfer in the blood compartment.

Small solute KoA is perhaps the most important piece of manufacturer-provided information available to clinicians when considering a dialyzer, as it a "lumped" parameter accounting for the effects of all three dialyzer components on diffusive clearance[10] (Fig. 6.4). In fact, the Ko component of KoA is the inverse of the Ro parameter described earlier. KoA is a function of blood flow rate, dialysate flow rate, and dialyzer clearance that is measured under the condition



• **Fig. 6.4** Relationship between blood flow rate, clearance, and KoA for urea (at constant dialysate flow rate).

of zero net ultrafiltration. It can be conceptualized as the maximum clearance obtained for a dialyzer of specific membrane surface area under the theoretical conditions of infinite blood and dialysate flow rates. Dialyzers having urea KoA values of at least 1000 mL/min (sometimes as high as 1500 mL/min) are routinely required for many patients to achieve delivered urea Kt/V values ≥ 1.2 per treatment in thrice-weekly HD.

The requirement of zero net ultrafiltration implies that KoA is a purely diffusive parameter, and this assumption is valid for all solute-membrane combinations with low-flux dialyzers. However, a zero net ultrafiltration condition is not equivalent to the absence of fluid fluxes across a high-flux dialyzer membrane and a condition of "pure diffusion" is not readily attainable with this type of device.[11] Small solute KoA values are minimally influenced under the condition of zero net ultrafiltration and remain valid solute removal parameters for high-flux dialyzers when measured in this context. However, diffusive KoA values for larger solutes (e.g., β_2-microglobulin: β2M) cannot be estimated reliably under these conditions, as the convective clearance associated with fluid fluxes ("internal filtration") contributes significantly to total clearance (see later). As such, KoA values for molecules other than urea and creatinine have little clinical meaning.

Membrane pore density has a substantial impact on dialyzer KoA for a particular solute/membrane combination, while membrane wall thickness is also an important determinant of diffusive removal rates. With increasing solute molecular weight, pore size limitations become increasingly important in providing restriction to solute entry and limiting ("hindering") diffusion for those molecules that gain pore entry.[12]

With regard to the dialysate compartment, flow velocities tend to be higher in the peripheral fibers due to some degree of channeling. A fiber packing density, defined as the ratio of the cross-sectional area comprised of fibers to the total cross-sectional area of the dialyzer casing; close to 60% seems to be adequate to minimize this phenomenon. Additional aids are interfiber spacing filaments and fiber undulation. These special features aim to provide homogeneous flow distribution in the dialysate compartment and avoid blood-dialysate flow mismatch that negatively affects

performance of the hemodialyzer.[13] In addition, they may enhance diffusive mass transfer by attenuating dialysate-side boundary layer effects.

Removal of Large Molecular Weight Uremic Toxins

During Hemodialysis

Convective Transport

As effective solute molecular weight increases, diffusive transport becomes increasingly limited. This limitation can be overcome by the introduction of convective transport, which relies on the mechanism of solvent drag.[14] In turn, the rate of convective solute removal is proportional to ultrafiltration rate. The parameter classically used to define the convective membrane transport properties for a specific solute is the sieving coefficient. The sieving coefficient is defined as the ratio between the solute concentration in the filtrate (C_F) and the solute concentration in the plasma water (C_P) under conditions of "pure" ultrafiltration (i.e., no dialysate flow)[8]:

$$SC = C_F/C_P \quad (6.2)$$

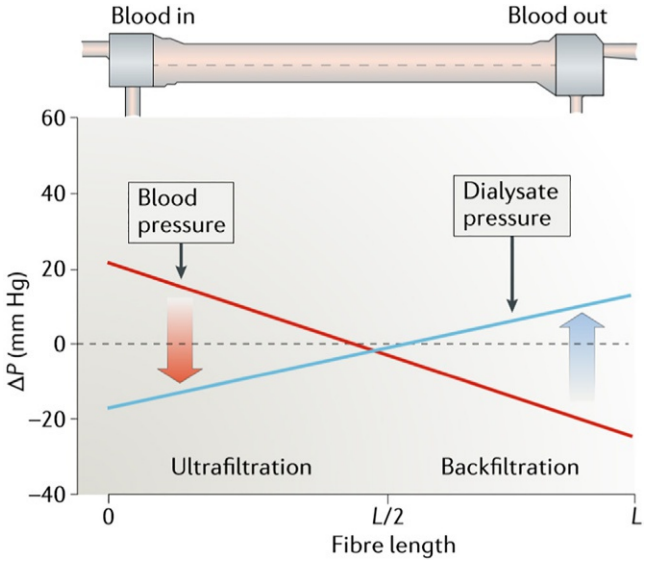
The observed (measured) sieving coefficient values are influenced by interactions that occur between the membrane and blood elements during dialysis. The nonspecific adsorption of a plasma protein layer, variously known as the secondary membrane, gel, or protein cake, reduces effective membrane permeability immediately upon exposure to blood[15]—this represents the process of fouling. With respect to the convective removal of specific solutes, the influence of secondary membrane formation is directly proportional to solute molecular weight. The proteins predominantly comprising this layer are those found in highest concentrations in the plasma, such as albumin, fibrinogen, and immunoglobulins.[16]

Other Mechanisms Influencing Large Solute Removal

Irrespective of flux, most dialyzers generally can provide sufficient small solute clearance rates to meet clinical requirements. However, current membranes, even those that have been considered traditionally to be highly permeable, provide limited clearance of compounds larger than 10 kDa for several reasons. Even though these membranes have relatively large mean pore sizes, they still offer substantial mass transfer resistance to the diffusive removal of large solutes. Moreover, fouling has a significant impact on convective solute clearances, especially for molecules larger than 10 kDa.[17] These constraints are particularly relevant under conditions involving high ultrafiltration rates, which promote secondary membrane formation by more effectively delivering plasma proteins to the membrane surface through convection (versus diffusion).

Under typical HD operating conditions, the water permeability characteristics for a standard high-flux dialyzer result in a relatively large drop in the axial (end-to-end) blood compartment pressure during treatment. The pressure drop is sufficiently large that, at some point along the length of the dialyzer, the blood compartment pressure becomes less than the dialysate compartment pressure under normal operating conditions. Thus, especially considering the oncotic effects in the blood compartment, there is a point at which ultrafiltrate begins to be driven from the dialysate to the blood as opposed to the "standard" (blood to dialysate) direction in the more proximal part of the dialyzer (Fig. 6.5). In fact, this combination of filtration and "backfiltration" is felt to be the predominant mechanism by which larger compounds are removed during standard high-flux HD.[18–20]

Another consideration with respect to large solute removal during high-flux therapies is membrane adsorption. Membrane composition and structure (pore size) influence adsorptive removal both qualitatively (i.e., the specific plasma proteins adsorbed) and quantitatively. The adsorptive removal of a low molecular weight protein (e.g., β_2 microglobulin) normally eliminated by the kidney is considered distinct from the more general process of secondary membrane formation for two reasons.[21] First, because the mass of large proteins, such as albumin, fibrinogen, and immunoglobulins, adsorbed during secondary membrane formation is a minute fraction of their circulating plasma pools, this process has no relevant effect on their plasma concentrations. Moreover, the adsorption of such compounds is limited to the nominal (blood-contacting) surface of the hollow fiber because they generally do not have access to the much larger surface area of the internal pore structure. As discussed subsequently, albumin is the exception to this general rule. On the other hand, adsorptive removal of smaller proteins that gain access to the large surface area of the internal pore structure can be quantitatively important, contributing to clinically relevant decreases in plasma concentrations during treatment. Significant amounts of β_2 microglobulin and other low molecular weight proteins can be absorbed by some membranes, contributing to a reduction in postdialysis concentration.



• **Fig. 6.5** Internal Filtration in a Highly Permeable Dialyzer.

New Approaches for Classifying Dialysis Membranes and Dialyzers

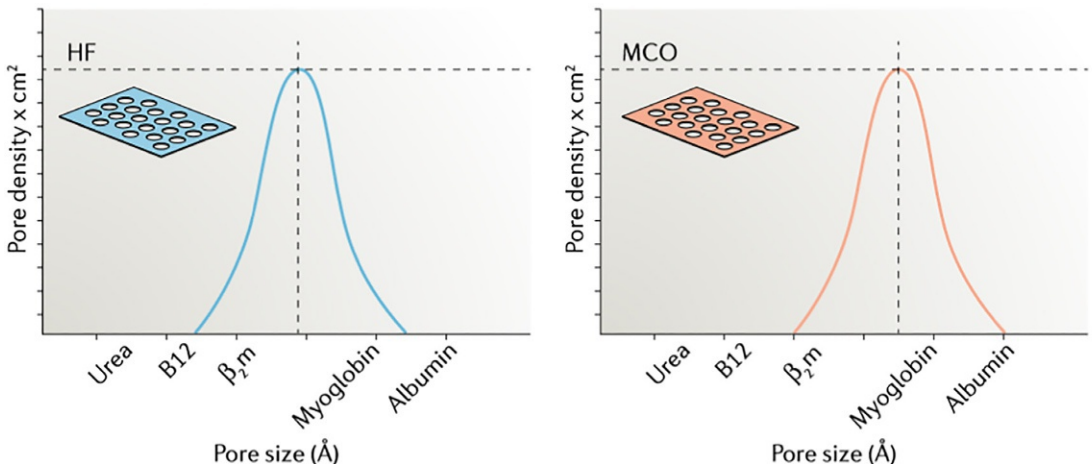
As more knowledge has been gained over the past several years about compounds contributing to uremic toxicity, it is clear that peptides, proteins, and protein-bound compounds comprise important categories.[22] However, as discussed, removal of such compounds may be relatively limited during diffusion-based therapies utilizing conventional high-flux dialyzers. In previous attempts addressing this limitation, "protein-permeable" membranes with larger mean pore sizes have been developed,[23] although excessive albumin losses were raised as a major concern. Nevertheless, these larger uremic toxins are generally considered to be clinically important, and more effective dialytic removal strategies may improve patient outcomes.

As new therapies are developed to address current limitations, membrane classification schemes also need to evolve. As mentioned, the most commonly used parameter for classification purposes remains Kuf, with a value of 12 mL/h/mm Hg differentiating low-permeability and high-permeability dialyzers according to the U.S. Food and Drug Administration. However, this regulatory (vs clinical) definition was based originally on the requirement of using a dialysis machine with an automated ultrafiltration control system in conjunction with a high-permeability dialyzer to avoid fluid balance errors. Since ultrafiltration control is now a standard feature of all dialysis machines, the clinical relevance of this definition is debatable. Moreover, it provides little insight into the depuration capabilities of a dialyzer—for instance, it does not recognize the category of high-efficiency dialyzers, which are primarily low flux and have small solute clearance rather than water flux as the defining criterion.[24]

Although still relatively rudimentary, a revised definition used for the HEMO Trial represented an improvement. In this definition, the two high-flux criteria were Kuf greater than 14 mL/h/mm Hg and first-use β_2 microglobulin clearance of greater than 20 mL/min, while a first-use β_2 microglobulin clearance of less than 10 mL/min defined a low-flux dialyzer.[25] (While mL/h/mm Hg is the unit for Kuf according to the U.S. Food and Drug Administration classification, this parameter is frequently normalized to membrane surface area, as indicated later). Finally, the European Dialysis (EUDIAL) Group defines a high-flux dialyzer as one having an ultrafiltration coefficient greater than 20 mL/h/mm Hg/m^2 and a β_2 microglobulin sieving coefficient greater than 0.6.[26]

Investigators most recently have proposed classification schemes focused even further on solute permeability properties. These new systems acknowledge the importance of larger molecules and the need to incorporate additional membrane classes that have extended removal spectra. Ward defined high-flux and "protein-leaking" dialyzers based on a combination of water permeability, β_2 microglobulin removal parameters (sieving coefficient/clearance), and albumin parameters (sieving coefficient/amount removed).[23] The high-flux class was defined by a water permeability of 20–40 mL/h/mm Hg/m^2, β_2 microglobulin sieving coefficient of 0.7–0.8, and albumin loss (based on a 4-hour HD treatment) of less than 0.5 gm while the same parameters defining a protein-leaking dialyzer were >40 mL/h/mm Hg/m^2, 0.9–1.0, and 2–6 gm, respectively. (Although not explicitly stated, these β_2 microglobulin values correspond to "virgin" membrane performance and are not reflective of potential diminutions during treatment as a result of secondary membrane effects.)

A higher permeability dialyzer class incorporating medium cutoff (MCO) membranes has been proposed more recently.[27] The goal of this dialyzer class is to enhance large solute removal (relative to standard high-flux dialyzers) by intentionally augmenting the extent of internal filtration through a combination of increased membrane permeability (pore size)[2] (Fig. 6.6) along with higher axial blood compartment resistance (decreased hollow fiber inner diameter).[28] Although standard high-flux membranes made possible the development of convective therapies, MCO dialyzers membranes represent the basis for a new diffusion-based therapy called expanded HD.[29]



• **Fig. 6.6** Comparison of pore size distributions for standard high-flux *(HF)* and medium cutoff *(MCO)* dialyzers.

Enhanced Large Uremic Toxin Removal: Clinical Considerations

Online hemodiafiltration (OLHDF) is now used widely in some parts of the world as an alternative to conventional (diffusion-based) HD. The primary rationale for using this therapy is increased removal of large molecular weight uremic toxins relative to conventional high-flux HD. One clinical concern with OLHDF is the potentially detrimental impact of significant albumin loss on a long-term basis. While adaptations in dialyzer design might be able to change the balance between large toxin removal and albumin loss in this therapy,[11] there is no clear consensus on a clinically acceptable limit for the latter. Nevertheless, albumin losses of up to 5 g per treatment for thrice-weekly treatment seem to be tolerated well by patients, although long-term evaluations are lacking.[29,30] In general, previous studies not surprisingly demonstrate a strong correlation between large solute and albumin permeability for high-flux dialyzers when operated in the diffusive and/or convective mode.

On the other hand, the recent efforts to extend the permeability spectrum of high-flux synthetic membranes may allow the presumption of the need for a convection-based therapy to be challenged.[31, 32] As mentioned, internal filtration is intentionally augmented for MCO and other dialyzers through increases in mean pore size and reductions in hollow fiber inner diameter. Recent preliminary data suggest this class of dialyzers has depuration capabilities approaching those of OLHDF without the need for (exogenous) substitution fluid administration.[32–34] Clinical outcome data for therapies made possible by this new class of dialyzers will help establish their role in the future, especially in relation to OLHDF.

Putting It All Together: Key Considerations

Because the use of (modified) cellulosic dialyzers for HD continues to shrink rapidly, this chapter has focused on dialyzers having synthetic membranes. A number of different types of synthetic dialyzers, all of which are generally considered to be biocompatible, are available for clinical use. For the prescribing clinician, rational treatment prescription requires an understanding of the basic mechanisms underlying solute and water removal in dialysis, namely diffusion, convection, adsorption, and ultrafiltration. With respect to small solutes, manufacturers frequently report clearances at various combinations of blood and dialysate flow rates. However, the most dependable parameter is urea KoA, which accounts for the three dialyzer elements (blood compartment, membrane, and dialysate compartment) that influence clearance. For larger solutes, manufacturers have traditionally reported sieving coefficients for larger molecules under conditions of "pure" ultrafiltration. However, such reporting does not capture all the factors influencing the removal of such compounds, especially internal filtration when a dialyzer is operated in the diffusive mode. New therapies utilizing membranes designed intentionally to produce high degrees of internal filtration are undergoing clinical evaluation as potential alternatives to standard high-flux and on-line convective therapies. Finally, the clinically acceptable degree of albumin loss for extracorporeal therapies remains to be defined, although an upper limit 5 g per treatment may be reasonable.

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7

Water Treatment Equipment for In-Center Hemodialysis

SCOTT BIEBER, DO

Introduction

During the provision of contemporary hemodialysis, the dialysate flows through the dialysate chamber of a dialyzer, which separates the toxic substances from the bloodstream into the dialysate via diffusion. The dialysate is composed of solute electrolytes in solvent water. In order to produce the final dialysate solution, a concentrated electrolyte solution is mixed with water. The ratio of concentrated electrolyte solution to water can vary based on many factors, including the type of concentration solution used and the proportioning system of the dialysis machine. In general, dialysate-proportioning systems mix around 1 part concentrate with 35–45 parts water. This final mixed dialysate is delivered to the dialyzer at a flow rate of 500–800 mL/min. Therefore, over a standard dialysis session, patients are exposed to vast quantities of water in the dialysate, that is, for a 4-hour session, anywhere from 120 to 192 L. To give you an idea of the magnitude of this volume, compare it with the estimated volume of total body water in a 70-kg man, which is around 42 L, with only 3.5 L of the total body water present in the plasma space. Therefore, dialysate water must be completely clear of potential contaminants to prevent injury to the patient during dialysis. Even contaminants found in dialysate water in small concentrations should be a cause for concern because their levels can reach toxic concentrations in the blood just by virtue of the vast quantity of water to which the blood is exposed. In addition, because of the absence of water contaminants in the blood, the diffusive pressure that can drive toxic solutes into the plasma space from the dialysate is high, and dialysis membranes do not offer selective protection to impede their entry from the dialysate into the bloodstream. Even contaminants in the dialysate that do not cross the dialysis membranes because of their size (e.g., bacteria) are found to be associated with systemic inflammation in dialysis patients. Systems that lack a separation of the blood from the treated water are available in some locations and demand an even higher level of water purity. For example, hemofiltration demands ultrapure or sterile water produced "on-line" for infusion into the bloodstream as replacement fluid. These mentioned considerations, among others, highlight the obligatory need for water purification methods that are effective and reliable in order to provide a safe dialysis therapy.

This chapter serves to highlight common contaminants found in municipal water sources that can be harmful to dialysis patients; it reviews the equipment used to prepare product water for use in the production of dialysate and covers some of the maintenance, monitoring, and design considerations for water treatment systems, as well as regulatory aspects that clinicians should be aware of when caring for dialysis patients. In addition, the reader is advised to consult guidelines published by the Association for Advancement of Medical Instrumentation (AAMI)/International Organization for Standardization (ISO), as well as their local governmental guidelines and regulations when considering water treatment systems for their dialysis patients. For the purposes of this chapter, we will focus on the most recently available ISO/AAMI guidelines, which are a product of the latest available knowledge and expertise. The content within may differ from local or governmental regulations, which tend to lag behind ISO/AAMI recommendations.

Water Contaminants

Water used for the production of dialysate fluid must meet a higher purity standard than what most municipal water supplies can provide. Because the production of dialysis water takes place in the dialysis facility or hospital, the responsibility for purification of water for dialysis rests on the dialysis provider. Common chemical contaminants in the water and their acceptable ranges are listed in Table 7.1. Contaminants can be present naturally in the water source, can be added to the water for specific purposes, or can enter

TABLE 7.1 Water Contaminant Acceptable Levels

Contaminant	Maximum Allowable Concentration
Contaminants with Documented Toxicity in Dialysis Patients (mg/L)	
Aluminum	0.01
Total chlorine	0.1
Copper	0.1
Fluoride	0.2
Lead	0.005
Nitrate (as N)	2
Sulfate	100
Zinc	0.1
Electrolytes Normally Found in Dialysate (mmol/L)	
Calcium	0.05
Magnesium	0.15
Potassium	0.2
Sodium	3
Trace Elements (mg/L)	
Antimony	0.006
Arsenic	0.005
Barium	0.1
Beryllium	0.0004
Cadmium	0.001
Chromium	0.014
Mercury	0.0002
Selenium	0.09
Silver	0.005
Thallium	0.002

ISO 13959, AAMI 2011.

the water at the level of the dialysis facility. Each of these sources of potential contamination should be appreciated and monitored. Because the contaminants present in water can vary over time, dialysis providers are encouraged to establish a relationship with local water authorities so that they are apprised of any changes to the water supply contents. Examples of substances added to water by water authorities that can be toxic to dialysis patients include chlorine and chloramines for the control of microbiologic growth, fluoride for dental prophylaxis, and alum, which can be used as a flocculent to decrease water turbidity. Chloramines can also be naturally present in water. Occasionally, lime is added to acidic or ion-poor water to raise the pH and prevent damage to metal piping systems or lead leaching from older piping systems. Other trace elements, organic matter, agricultural products such as pesticides and fertilizers, and industrial products can also work their way into the water supply. Metals such as lead and copper can leach from plumbing systems. Microorganisms such as bacteria, fungi, protozoa, endotoxins, and other microbiologic fragments can also be present in water. Knowing the source of the water in your dialysis unit can help you anticipate which contaminants are more likely to be present. For example, water from surface sources such as rivers, lakes, and reservoirs is more likely to be ion poor (low conductivity) but is more prone to having organic surface contaminants present in it, such as particulates, pesticides, and others. Water that is derived from an aquifer or well tends to have more inorganic or ionic contaminants present (high conductivity), which the water accumulates as it percolates down through various sedimentary layers. Occasionally, city water authorities issue boil water advisories when water is excessively contaminated with microorganisms. Care should be taken to vigilantly monitor the water treatment system at this time. If the water treatment system is equipped with a reverse osmosis (RO) membrane, then dialysis can continue because this membrane will serve as a bacterial and endotoxin barrier. However, if a deionizing system is used, then ultrafilters or bacterial and endotoxin retentive filters downstream of the deionization (DI) system should be in place to prevent exposure to patients. Municipalities can often treat the water with higher concentrations of chlorine and chloramines during periods of infection, and care should be taken to make sure that the absorptive effect of the carbon tanks is not overwhelmed, thus causing spillover of chlorine and chloramines into the product water.

Exposure to these various contaminants in the water when in high concentrations can present a catastrophic nature, with multiple patients on dialysis being affected simultaneously. Sudden onset of illness in multiple patients, in particular, symptoms of hemolysis and intoxication, should prompt consideration of water or dialysate contamination. Episodes of hemolytic anemia involving multiple patients have been witnessed in dialysis units where carbon tanks were exhausted or overwhelmed, sometimes during times of system upgrades or increased water demands. Exhausted DI systems have been linked to copper and fluoride exposures. Exposures to disinfectants such as hydrogen peroxide and formaldehyde can result from incomplete or improper rinsing of water treatment systems after the disinfection procedure. Deleterious exposure to metals such as copper, lead, or brass in piping, fittings, valves, or aluminum in pumps used to transfer concentrates has occurred in case reports. Although case reports highlight drastic incidents of water contamination, it should also be recognized that exposure to contaminants in lower concentrations can manifest in atypical and subtle ways, which can be missed by health care providers. For example, chronic exposure to bacterial fragments like endotoxin may present with signs of systemic inflammation that are difficult to distinguish

from other disease processes. Table 7.2 lists some of the common water contaminants and the symptoms that they can cause.

Water purification systems in dialysis units should take care to address each potential contaminant in the source water. Equipment used for water purification should be designed with knowledge of the contaminants that are present in the source water. Tables 7.3 and 7.4 contain some suggested steps to take when planning a new water system and considerations for water system design. Table 7.5 provides a list of considerations to take into account regarding the maintenance and monitoring of water treatment systems.

TABLE 7.2 Signs and Symptoms of Water Contamination

Contaminant	Signs and Symptoms of Exposure
Aluminum	Intoxication, seizures, neurologic symptoms, bone disease, anemia
Calcium	Confusion, lethargy, nausea, vomiting
Copper	Hemolysis, acidosis, nausea, seizure, shock
Chlorine/ chloramines	Hemolysis, methemoglobinemia, hyperkalemia, cardiac arrest
Fluoride	Intoxication, pruritus, headache, nausea, chest pain, ventricular fibrillation
Lead	Neuropathy, anemia, abdominal pain, confusion, seizure
Nitrate	Methemoglobinemia, cyanosis
Sodium	Hypertension, thirst, pulmonary edema, confusion, seizure
Sulfate	Nausea, vomiting, chills, fever
Zinc	Nausea, vomiting, fever, anemia

TABLE 7.3 Steps in Developing Specifications for a Water Treatment System

Step	Procedure
1	Determine applications for which water will be used. Estimate water consumption and required delivery pressures.
2	Define product water quality for each application.
3	Evaluate the quality of feed water.
4	Compare feed water quality with required product water quality and determine the reduction needed for each contaminant.
5	List water purification options and determine the preferred system configuration.
6	Prepare request for bids.

TABLE 7.4 Questions to Be Considered in Configuring a Water Treatment System

Step	Procedure
1	What purification processes are needed to produce water of the required purity?
2	How should the processes be sequenced to maximize efficiency and minimize maintenance?
3	How should the feed water be pretreated to prolong the life of the major purification equipment?
4	Is a supplementary water heater needed to maintain feed-water temperatures in the winter?
5	Should the distribution system include a storage tank?
6	What is the planned method of sterilization of the water treatment system?

Equipment Used for Water Purification

Multimedia Filter (Fig. 7.1)

The purpose of the multimedia filter, also known as the sediment filter or depth bed filter, is to remove particulate matter from the source water. Plant debris, rocks, rust, silt, clay, and other debris are removed from water as it passes through the multimedia filter. Multimedia filters are usually composed of layers of gravel, sand, and anthracite. The water passes from larger gravel to finer sand and anthracite as it moves through the filter tank. Bigger particulate matter is trapped in the initial gravel layers, and smaller particulates are trapped in the finer layers of sand and anthracite. Most multimedia filters are capable of removing particulate matter down to 10 microns in diameter. In some ways, this mechanism of water filtration is similar to what happens in nature as groundwater filters down through the water table into an underground aquifer. The multimedia filter is usually the first filter that source water passes through. It is a necessary component of the water treatment system for the protection of the downstream water treatment components. For example, if particulate debris is not removed from the source water, it can end up fouling or damaging the RO membrane.

Monitoring the Multimedia Filter

- With use, the multimedia filter can become obstructed with debris. To prevent this, the filter is backwashed daily at a time when patients are not on dialysis.
- Pressure gauges should be present pre and post filter to measure the difference between the two. If the filter is occluded with debris, the pressure drop will increase. The pressure difference (delta) across the filter should be monitored regularly. Trends in pressure changes should be established and investigated if abnormal.

TABLE 7.5 Water System Monitoring

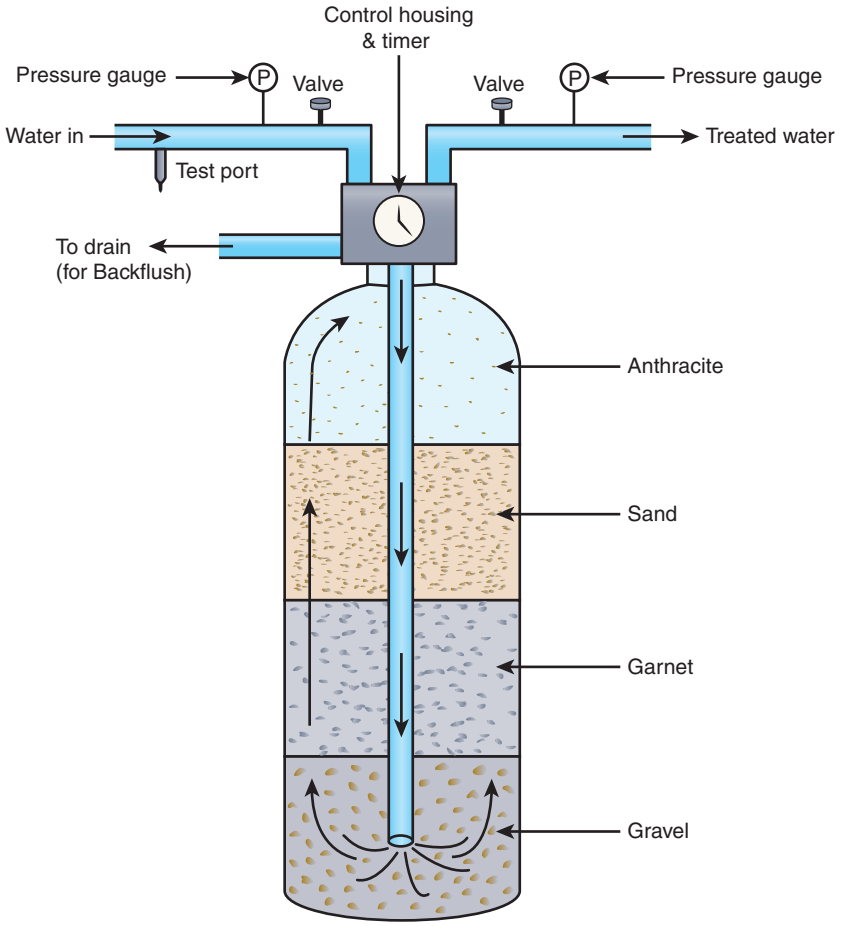
Test	Acceptable Level	Recommended Frequency of Measurement
Total chlorine	≤0.1 PPM	Measured at the start of the day and every 4 hours
Free chlorine	<0.5 PPM	Measured at the start of the day and every 4 hours
Chloramine	<0.1 PPM	Measured at the start of the day and every 4 hours
Hardness	<1 GPG (17 PPM)	Measured at the end of every day
Component inflow vs outflow pressure delta	>10 mm Hg above baseline	Daily, delta trends compared with previous measurements and with baseline/initial values
EBCT	>10 min	Monthly and with any change in flow or carbon volume
Loop flow velocity	>3 ft/s (indirect) >1.5 ft/s (direct)	Daily, measured at the end of the loop when operating under peak demand
Water analysis (source/tap water and treated water)	See Table 7.1	Quarterly (annually at a bare minimum) Whenever water authorities change the composition of water or when the source of the water changes When the RO is installed When RO membranes are changed When % rejection drops below 90% (When performing water analysis, always recalculate RO alarm set points)
Colony count/total viable microbial count (TVC)	See Table 7.6	From loop: first station and last station in loop monthly. All stations at least once annually. RO and storage tanks at least quarterly, monthly is preferred. Dialysate: at least two machines monthly, every machine at least once annually
Endotoxin	See Table 7.6	Same as for colony count
Percent rejection	Based on water analysis, usually >90%	Continuously measured by RO
Percent recovery	Depends on facility, based on trends	Continuously measured by RO
DI resistivity	>1 MΩ·cm	Continuously measured by DI resistivity meter
UV energy output	>30 mW·s/cm^2 (>16 mW·s/cm^2 if UV calibrated meter)	Monthly, more frequently if nearing the end of the life span of the UV bulb

DI, Deionization; *EBCT*, empty bed contact time; *GPG*, grains per gallon; *PPM*, parts per million; *RO*, reverse osmosis; *UV*, ultraviolet.

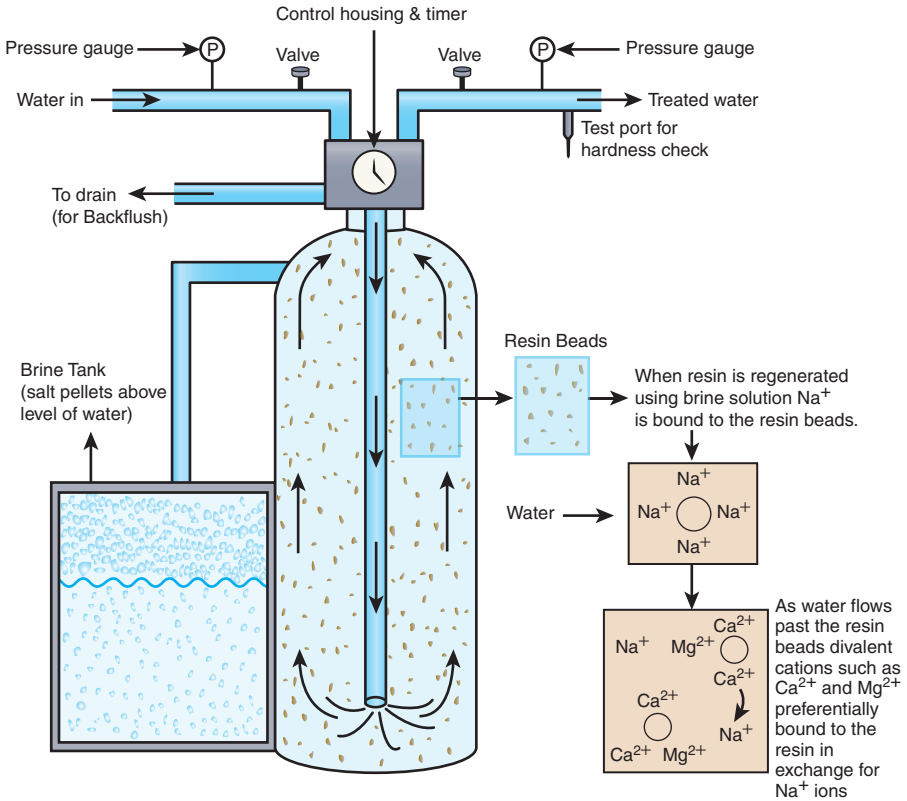
- Pressure delta of >10 mm Hg above baseline across the multimedia filter indicates a problem.
- If automated systems are used for backwashing the filter, backwash timers should be monitored regularly to ensure that rinsing of the filter occurs during off-hours when patients are not on dialysis.

Water Softener/Brine Tank (Fig. 7.2)

Groundwater can accumulate calcium and magnesium as it percolates through deposits of limestone or chalk. Water that has large amounts of calcium and magnesium can leave behind hard residue or scale. One example of this left-behind residue is water spots on a glass shower door. The hardness of water refers to its overall content of polyvalent ions that cause this scale, the major contributors being divalent calcium and magnesium. The process of "softening" the water is often accomplished by the exchange of calcium and magnesium ions for sodium ions. Calcium and magnesium ions will be effectively removed through RO; however, the softening process is essential prior to water reaching the RO unit to protect membranes from damage due to scaling. Additionally, in the case of systems that use DI to form product water, the presence of large amounts of divalent ions can overwhelm the deionizer resin beds, leading the to release of other toxic ions into the treated water. Water softener units are typically composed of a tank that holds ion-exchange resin and is connected to a brine tank. As water moves through the softener tank, the resin releases sodium ions in exchange for higher-affinity divalent



• **Fig. 7.1** Multimedia Filter. The typical layout of a multimedia filter allows for the movement of water through a bed of particles of declining size. Multimedia filters are designed to trap particulate debris found in source water.



• **Fig. 7.2** Water Softener. Water softeners remove "hard" divalent ions such as calcium from the source water in exchange for "soft" sodium ions. Cation exchange resin is utilized to trap calcium ions. Supersaturated sodium solution from the brine tank is utilized to recharge the cation exchange resin.

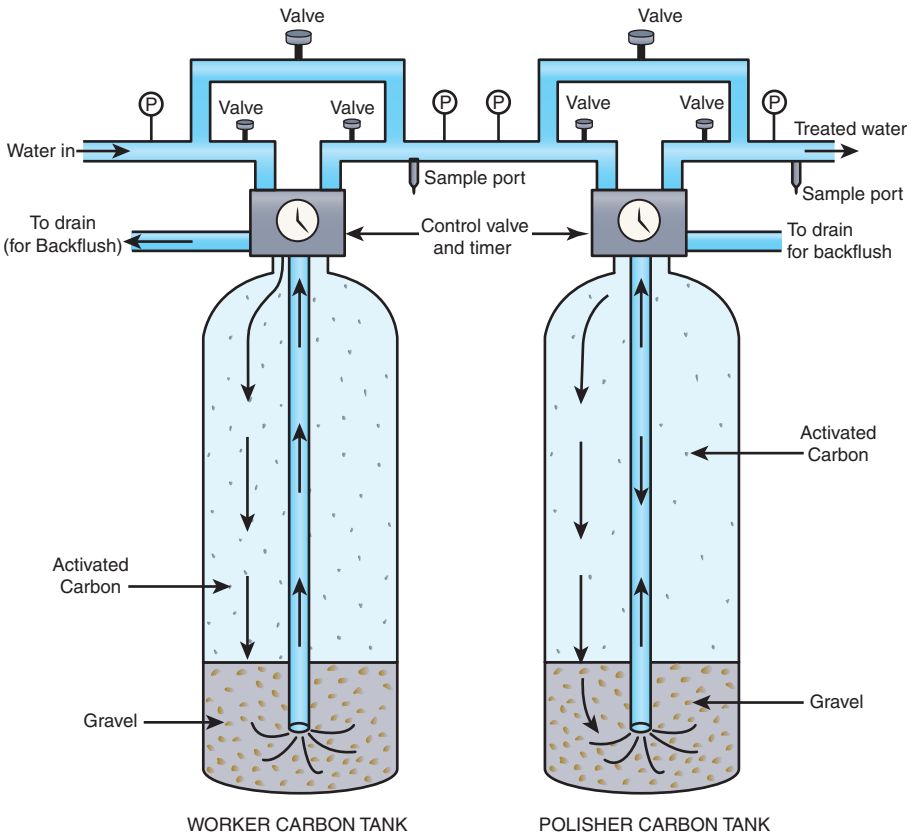
calcium and magnesium. The brine tank is used to hold a concentrated sodium chloride solution. Regeneration of the resin in the softener is accomplished by overcoming the affinity of the resin beads for polyvalent cations with a supersaturated sodium chloride solution from the brine tank. Recharging can be initiated on a timed basis or after a monitor, which measures a certain amount of water processed, indicates the need. Recharging should take place at a time when patients are not dialyzing to prevent accidental spillage of hypertonic sodium chloride solution into the water treatment system.

Monitoring the Water Softener

- Measurement of water hardness in grains per gallon (GPG) or parts per million (PPM) is used to monitor the efficiency of the water softener.
- Water hardness can be measured on site using colorimetric test strips. Personnel performing the testing should be able to distinguish between the colors on the test strips. There should be a well-labeled water sample port post water softener for the measurement of hardness.
- Source water hardness should be compared with treated water hardness periodically.
- After treatment by the water softener, the water should measure 1 GPG (17 PPM) or less.
- The hardness should be checked at the end of the day so that the capacity of the water softening system is fully appreciated.
- The brine tank should be checked daily to ensure that the solution is adequately supplied with sodium chloride (e.g., salt pellets are above the level of the water and are not forming a salt bridge).
- Pressure drop across the softener should be monitored regularly. A pressure change of > 10 mm Hg above baseline suggests a problem with the resin bed.
- Regeneration of the softener resin should take place during a time when patients are not on dialysis.
- Timers set for automatic softener regeneration should be monitored to ensure that regeneration does not occur during facility operating hours. There is potential for a high concentration of sodium to enter the water if regeneration occurs during dialysis treatments. Conductivity monitors on the RO system should sound an alarm if a high sodium concentration is detected; however, they should not be relied upon exclusively.

Carbon Tanks (Fig. 7.3)

Activated carbon is used in water treatment systems to remove chlorine and chloramine from water. These agents are commonly added to the water supply by municipal authorities in small quantities in order to prevent microbiologic growth. Failure to remove chlorine and chloramines from treated water can lead to severe hemolytic anemia in patients on dialysis. Free chlorine has been known to degrade certain RO membranes, leading to holes in the membranes



• **Fig. 7.3** Carbon Tanks. The typical carbon tank layout has two tanks in series (worker followed by the polisher). The function of the carbon tanks is to remove chlorine and chloramines from the source water.

and failure of appropriate filtration. Not all forms of carbon are equivalent. Powdered activated carbon has a large surface area in a smaller volume but is more prone to channeling and pressure problems, which can reduce effectiveness. Granular activated carbon or catalytic carbon systems are more commonly used. Typically, water treatment systems are designed with a redundancy by placing two carbon tanks in series. The first tank is commonly referred to as the "worker" carbon. The second tank in the series is known as the "polisher" carbon. The amount of carbon in the tanks must be considered in relation to the expected water flow through the tanks in order to ensure that there is a minimum of 5 minutes of contact time with the carbon for each tank or a total minimum of 10 minutes of contact time at the maximal expected water flows. Empty bed contact time (EBCT) can be used as an indirect way to estimate the contact time between the water and the carbon bed and is calculated using the following formula:

$$\text{EBCT} = V / Q,$$

where V is the volume of carbon in the tank and Q is the flow rate. This equation can be used to calculate the EBCT in existing water treatment systems. Typically, calculations would be done for a "worst-case scenario" where every machine in the dialysis unit is in use and demanding the maximum amount of water for production of dialysate, and the Q in the equation would reflect the maximal flow needed to deliver water at the highest possible level of demand. In that way, even when water demands are stretched to capacity, an EBCT of at least 10 minutes is ensured. Using units of cubic feet for volume and cubic feet per minute for flow, converting to gallons, and solving for V yields the following equation:

$$V = (Q * \text{EBCT}) / 7.48,$$

where 7.48 is the number of gallons in one cubic foot of water and Q is the flow rate in gallons per minute (GPM). This equation can be used when planning a water treatment system to estimate the volume of carbon you will need in the carbon tanks in order to achieve your EBCT goal of at least 10 minutes. Solving the previous equation for EBCT, one can calculate the EBCT under conditions of varying flow rates. This becomes important to do periodically because flow rates through RO membranes can change over time as the membranes age or with changing water conditions. For example, flows through RO membranes usually speed up in summer months as the water warms and becomes less viscous. This increase in flow through the RO can pull water through the carbon tanks more quickly and lead to decreased EBCT. EBCT must be calculated at least monthly to ensure changes over time are appreciated.

Monitoring the Carbon Tanks

- Testing for chlorine and chloramine is performed to monitor the function of the carbon tanks.
- The allowable limit for chlorine is 0.5 PPM and for chloramine is 0.1 PPM.
- There is no way to test directly for chloramines. Indirectly, it can be measured by comparing the difference between the total chlorine and free chlorine.

$$\text{chloramine level} = \text{total chlorine level} - \text{free chlorine level}$$

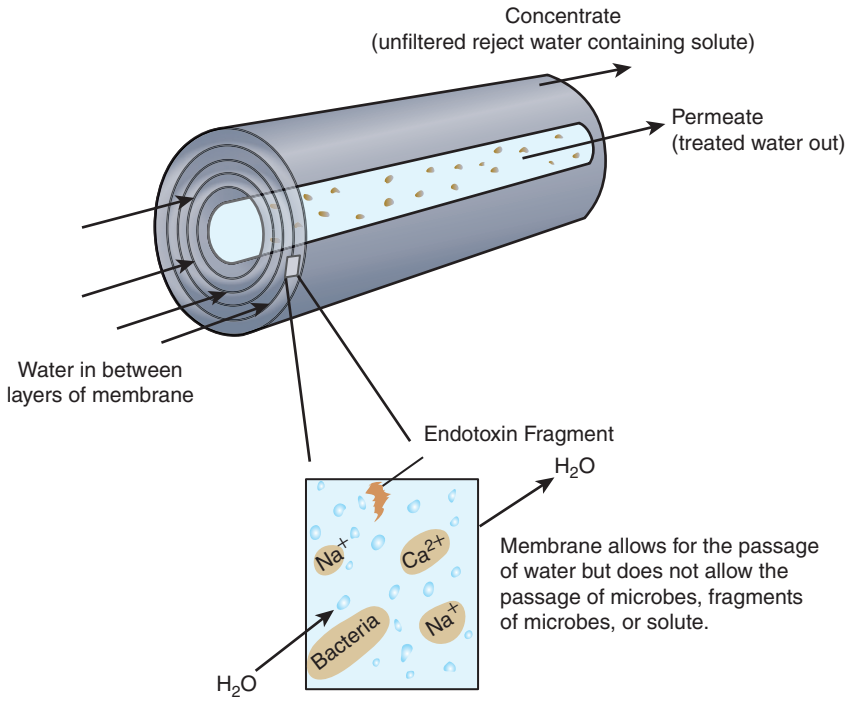
- Most dialysis facilities do not check both free and total chlorine. It is acceptable and simpler to test only total chlorine with an allowable limit of < 0.1 PPM.
- Chlorine tests are usually done with colorimetric strips. Personnel performing the tests should be able to distinguish differences in color change.
- Alternatively, online monitors can be used in accordance with manufacturer's specifications.
- The testing should be done after the first carbon tank (worker) from a well-labeled sample port. If the worker sample is not acceptable, then the water should be tested from a sample port following the second carbon tank (polisher). If the polisher sample is acceptable, then dialysis can continue but plans should be made to replace the failing worker carbon tank, and consideration should be given to increasing the frequency of testing while running on a single tank. If the sample post polisher does not meet the allowable limit, then dialysis cannot continue until the problem is fixed.
- Testing should be performed at the start of the day and at least every 4 hours while patients are on dialysis. Some facilities elect to test water every 3 hours as a practical way to make sure that the timing of their sample collection always comes in under the 4-hour limit.
- Testing at the start of the day should occur after allowing the system to run for 15 minutes. This is so that water that has dwelled in the water treatment system or carbon tanks overnight is fully expelled and the sample tested reflects active flow of new water through the tanks.
- The carbon tanks must supply an EBCT of at least 10 minutes. The EBCT should be calculated periodically to ensure that the goal is met. Typically, this is done on at least a monthly basis using current water flow rates. In addition, situations that lead to changes in water flow (such as when adding stations to a unit) or carbon tank volume should prompt a recalculation of the EBCT.
- Pressure drop across each of the carbon tanks should be monitored with > 10 mm Hg difference above baseline, suggesting a problem, such as fouling of the tank with particulate matter.
- Back-flushing of the carbon tanks should occur during hours when the facility is not in operation. Timers set for automatic back-flushing should be monitored regularly to ensure that they are set to the correct time.
- The risk for patient injury when the carbon tanks fail is high. Therefore, rigorous monitoring and routine recording and review of the function of the carbon tanks are mandatory.

Reverse Osmosis (Fig. 7.4)

RO is a process by which pressure is used to force water through a tight membrane that blocks the passage of solute, particulate matter, bacteria, and endotoxins, among other things, to produce pure water. The water that is filtered by the RO membrane is called product water, permeate, or filtrate. The leftover water and solute that do not pass through the membrane are referred to as reject water, wastewater, or concentrate. The term "osmosis" describes the movement of water that occurs when two compartments are separated by a semipermeable membrane whereby water moves from an area of low solute concentration to an area of high solute concentration. During the RO process, water is forced in the opposite direction or against an osmotic gradient by using pressure, thus the term "reverse osmosis." The amount of energy or pressure needed to overcome osmotic pressure depends on the ionic content (conductivity) of the source water. The RO system will require roughly 10 psi per 1000 PPM of solute. Thus, RO is very reliant on energy to produce a pressure gradient across the membrane, and the amount of energy required will increase with increasing conductivity of the source water. RO systems typically consist of prefilters, pumps, flow and pressure controls, membranes (typically spiral-wound membranes), and various monitors. As water flows parallel along the membrane, a portion of the water is forced through the membrane and into the product water stream, whereas the remainder that does not pass the membrane is directed to the drain or recycled. Orienting the flow of permeate and concentrate in this way allows for a natural process of continuous flushing of the membrane and avoidance of membrane fouling. Some RO systems will recycle the rejected water stream and reroute it past the membrane to increase velocity through the membrane system and further prevent membrane fouling or failure. RO systems are very effective at producing water appropriate for dialysate production; however, they are complicated systems that require close monitoring and regular maintenance. The efficiency of the RO system is affected by a number of factors, including pressure in the system, composition of the feed water, temperature of the feed water, and level of dissolved gases (bubbles) in the feed water. Often, water treatment systems are designed with redundancy by placing two RO units in the water treatment system. This is known as a "double-stage" RO system. Whether or not a double- or single-stage RO system is necessary depends in large part on the quality of the source water. In most cases where source water is of reasonable quality, double-stage RO systems are not necessary to produce pure water, but they are still desire for the purpose of supplying redundancy. In the event that one RO is not functional, the other RO can be utilized, and patient care can continue. Alternatively, some water treatment systems will use RO as the primary method of water treatment and DI systems for polishing or as a backup in case of failure of the RO.

Monitoring the RO System

- Pressure and flow are measured at various points in the RO system to ensure proper function.
- Conductivity is used to monitor the removal of solute by the RO system. Conductivity describes the ability of the



• **Fig. 7.4** Reverse Osmosis. The reverse osmosis membrane typically has a tight spiral configuration that allows water to pass but traps solute particles. The permeate is the purified water, and the concentrate is the waste or brine solution.

water to conduct electrical charge. If more dissolved solute is present, water will conduct electricity more readily.
- The conductivity of product water from the RO is monitored continuously during RO operation and often displayed as total dissolved solids or TDS.
- The percent rejection of an RO system describes the ability of the system to remove solute, thus reducing conductivity in the product water, and can be thought of as the percentage of solute that was removed from the water during RO. The percent rejection is calculated using the following formula:

$$\%\ \text{rejection} = \left[\left(\begin{array}{l}\text{feed water conductivity-}\\ \text{product water conductivity}\end{array}\right)/\ \text{feed water conductivity}\right] * 100$$

- Modern RO systems will monitor and display the percent rejection in real-time during operation.
- There is no absolute value that is desirable for the percent rejection. Rather, the dialysis facility should use the percent rejection to monitor the efficiency of the RO over time.
- The dialysis facility should take into account the source water composition, the percent nominal passage through the RO of each of the water contaminants with the given RO specifications from the manufacturer, and the composition of the treated permeate water and, based on these values, calculate the lowest percent rejection at which the treated water still meets AAMI requirements as listed in Table 7.1. Alarms set points can then be established on the RO system when the desired percent rejection or conductivity is not achieved.
- Percent recovery (also known as the water conversion factor) can be used to monitor the performance of the RO system. The percent recovery can be calculated using the following formula, where Q is the flow rate:

$$\%\text{recovery} = \left[\begin{array}{l}\text{permeate } Q\ /\\ \left(\text{permeate } Q + \text{reject } Q\right)\end{array}\right] * 100$$

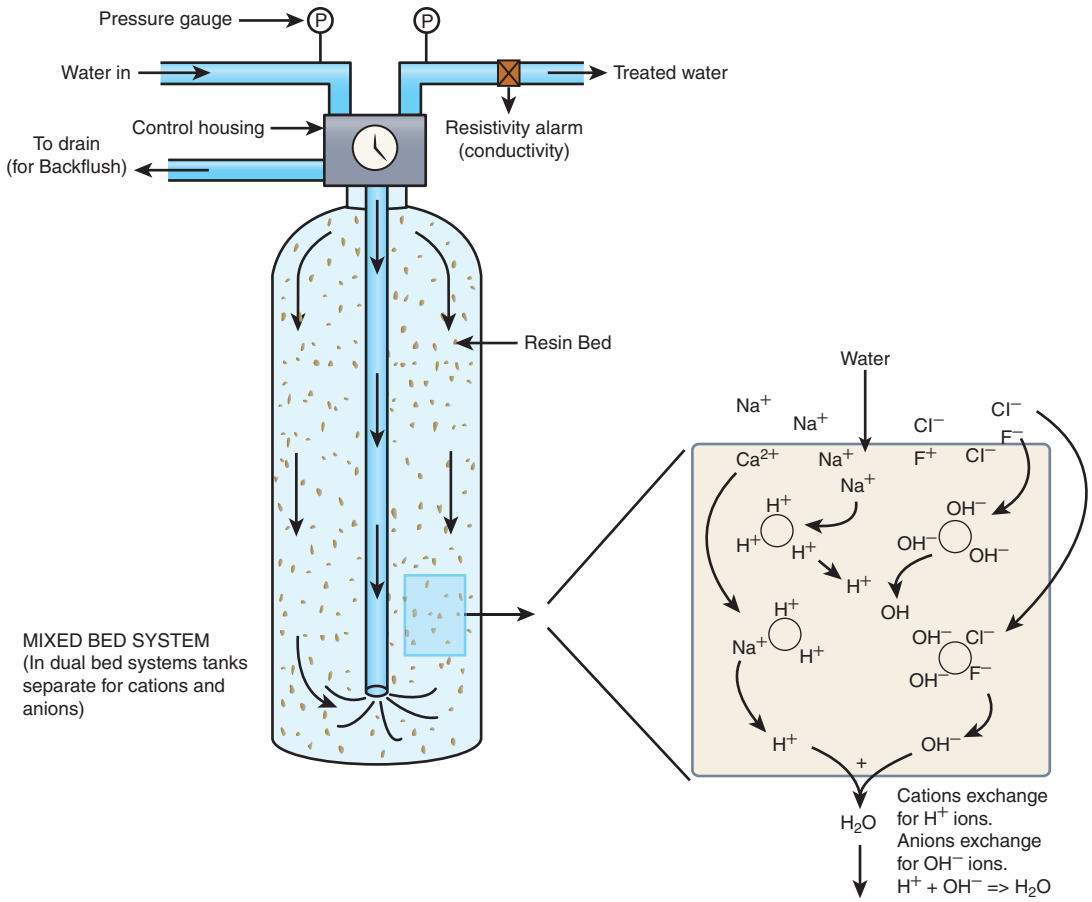
- The percent recovery does not inform water quality. Rather, it is useful for trending the performance of the RO membrane. Membranes that become fouled over time will drop their percent recovery. Permeate flow rate can vary due to changes in pressure and temperature as well. For example, a seasonal decrease in water temperature would be expected to decrease the percent recovery.
- The various measures of RO function—pressure, flow, conductivity, percent rejection, percent recovery, etc.—should be recorded in a daily treatment log for regular review and trending analysis.

Deionization (Fig. 7.5)

DI is a method by which water can be purified of cationic and anionic components using exchange resins. The resins in DI systems are essentially beads with either hydrogen (H^+) cations attached or hydroxyl (OH^-) anions attached. When higher-affinity cations from the feed water come in contact with the cation resin, H^+ ions are released, and the higher-affinity cation is bound to the resin. Likewise, when anions in the feed water come in contact with the anion resin, OH^- anions are released, and the anion is bound to the resin. Subsequently, H + and OH^- are available to combine and form pure water (H_2O). DI systems can be set up in a two-stage process as dual-bed systems, where the cation and anion resins reside in separate tanks, or as mixed-bed systems, where the resins are combined in a single tank. Most commonly, deionizer systems consist of two mixed-bed systems in series with resistivity or conductivity monitors following each unit. The DI system for dialysis water, when operated and maintained correctly, can provide product water of high quality. However, there are several limitations to deionizers. Deionizer systems have a limited life span. Once ionic resin sites are saturated, product water can become contaminated. This is because ions of lesser affinity, which are not H^+ or OH^-, can be released from the resin in exchange for higher-affinity ions. Multiple cases have been reported where anionic resin was depleted, and fluoride (F^-) ions were released into product water as chloride (Cl^-) and other anions bound with the resin in higher affinity and displaced the F^- ions, leading to fluoride intoxication in the dialysis unit. Even partially exhausted DI resins can be a source of water contamination. Therefore, close monitoring of these systems is essential to protect patient safety. Exchange resins need to be regenerated periodically to prevent contamination from happening. During the regeneration process, strong acid and strong base are added to the ion beds to regenerate the resin with H^+ and OH^- ions and flush out previously bound ions. Unlike RO systems, DI systems do not effectively remove particulate matter, bacteria, endotoxin, and other organic materials from the source water. Therefore, DI systems must be combined with other water treatment components. In particular, DI systems can serve as a breeding ground for bacteria. Deionizers that are used as backup systems can have absent or reduced water flow and are particularly prone to bacterial contamination. Downstream ultrafilters or cartridge filters capable of retaining endotoxin and fine resin debris should be in place to protect the loop from bacterial contamination originating in the DI tanks.

Monitoring the DI System

- Deionizers are monitored continuously using a resistivity meter. Resistivity is the inverse of conductivity and describes the opposition of water to electrical current. The higher the resistivity, the more pure, or solute-poor, the water.
- Treated water should have a resistivity of 1 MΩ cm or more. Water with resistivity less than 1 MΩ cm should not be used. Pure water has a resistivity of around 18 MΩ cm. Resistivity monitors should be equipped with alarms to alert staff when resistivity is not appropriate. There should be an automatic divert to drain if the resistivity drops below 1 MΩ cm.
- Resistivity should be recorded at least twice daily and trends reviewed regularly.



• **Fig. 7.5** Deionization. Mixed-bed deionization systems contain cation and anion exchange resins that bind solutes in the water in exchange for hydrogen (H+) and hydroxide ions (OH–), which go on to form pure water (H_2O). In dual-bed systems (not shown), cation and anion exchange resins are in separate tanks.

- Deionizer systems are prone to contamination with bacteria and should be monitored closely for microbiologic contaminants.
- Pressure pre and post deionizer should be monitored. A pressure drop of > 10 mm Hg above baseline can indicate deionizer fouling with particulate matter or resin breakdown.

Ultrafilters/Cartridge Filters/Endotoxin Retentive Filters

Ultrafilters can be placed at various points in the water treatment system to filter out particulate matter, which happens to escape earlier filtration or debris from components in the system themselves (e.g., "fines" from the carbon tanks) or to filter out bacteria and endotoxins. An ultrafilter designed for endotoxin removal may be rated to achieve complete endotoxin removal with a pore size ranging from 0.001 to 0.05 microns in diameter. Ultrafilters are often rated by size for a given flow and can slow the flow velocity through the water treatment system. Consideration to expected flow needs to be given when designing and selecting ultrafilters for the water treatment system. The housing of the ultrafilter should be opaque to prevent light from promoting algae growth. Ultrafilters should be exchanged on a scheduled basis to prevent failure due to fouling or microbial contamination.

Monitoring Ultrafilters

- Ultrafilters can become fouled with debris over time, which increases the pressure drop across the filter.
- Measure pressure drop on inlet and outlet lines, comparing with recommendations from the manufacturer. Filters with large pressure drops will need to be exchanged.
- The measured pressures should be recorded daily and trends routinely analyzed.

Ultraviolet Lights

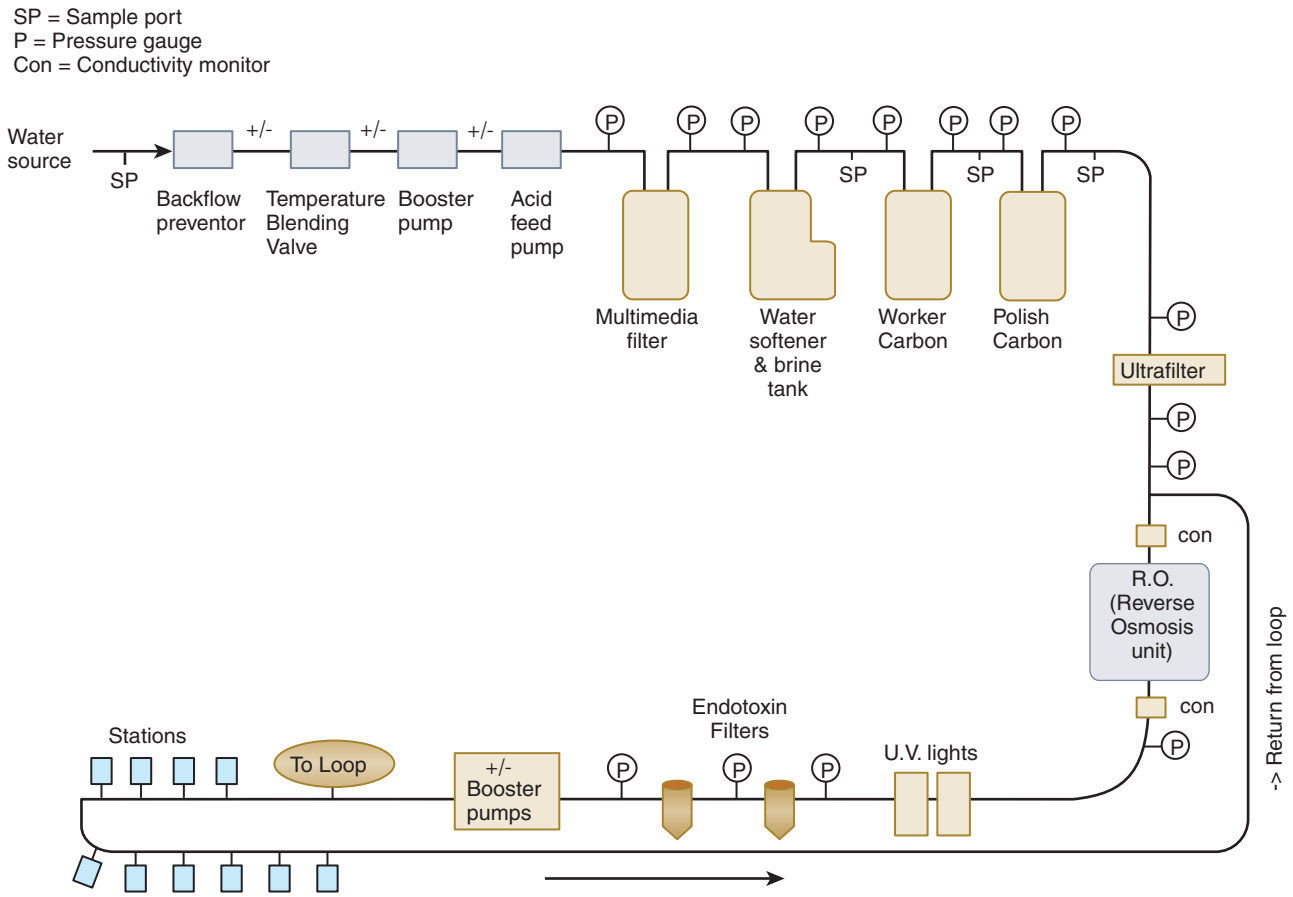
Ultraviolet (UV) light can be used in a water treatment system to control microbiologic growth. UV lights typically are composed of a quartz glass sleeve through which the water flows, with a UV bulb overlying the sleeve. It is recommended that the UV light is applied at a wavelength of 254 nm and provides 30 $mW{\cdot}s/cm^2$ of energy. UV light housings should be opaque. The UV lights are rated for flow. Thus, flow that is too fast may not allow for effective exposure of the water to UV light. When properly functioning, UV lights are capable of killing all potential free pathogens in the water stream, but it is important to recognize that UV light may not be effective in treating organisms embedded in biofilm. UV lights should be followed by an ultrafilter that is capable of retaining bacteria and endotoxin.

Monitoring of UV Lights

- UV lights are monitored with a radiant energy meter that measures on-line energy intensity and is capable of alarming if the intensity is not sufficient.
- If the irradiator is not fitted with a calibrated UV intensity meter that is filtered to restrict its sensitivity to the disinfection spectrum, the dose of radiant energy provided by the lamp should be at least 30 $mW \cdot s/cm^2$. If it does have a calibrated meter, the minimum dose of radiant energy should be at least 16 $mW \cdot s/cm^2$. This requirement is meant to prevent the development of microbial resistance.
- UV light intensity checks should be recorded daily and routinely reviewed.

Water Distribution Loop (Fig. 7.6)

The ideal water distribution loop would be composed of a biocompatible material that does not leach into the water, is smooth without ridges or gaps, and does not have any dead space where water is left stagnant. Accomplishing these criteria will promote flow velocity and prevent microbiologic adhesion and biofilm formation. Systems should be designed with the least amount of joints and fittings possible. Gradual bends are preferred over 90-degree turns. Flow through in the loop ideally should be at least 3 ft/s to prevent bacterial biofilm formation. Piping systems and fittings can be made of polyvinyl chloride (PVC) or cross-linked polyethylene (PEX), among other materials. Care should be taken to understand the means of disinfection and how that affects the piping materials. For example, PVC is not compatible with heat sterilized disinfection systems. Water should run through the loop continually, Therefore, points of connection for the dialysis machine to the water source ideally would be designed as a loop with continuous flow and minimal dead space. Two types of water distribution loops include direct feed systems and indirect feed systems. Fig. 7.5 illustrates a direct feed system. With direct feed, there is no storage tank; water runs through the system directly to the loop. Water that is not consumed in the loop then returns back to the RO. In an indirect feed system, there is a storage tank that holds water, which is then pumped to the loop. Water not used in the loop then returns to the storage tank. The direct feed system can be simpler in that it does not require the storage tank and extra components that the storage tank demands. However, it has to be designed carefully with water needs in mind, and all components of the water treatment system need to be able to keep up with demand at peak times. Depending on the size of the unit, this sometimes makes direct feed systems impossible. In indirect feed systems, water can be produced and stored to meet demand at peak times, thereby overcoming this limitation. However, the presence of a large storage tank provides another source for microbiologic contamination of the loop.



• **Fig. 7.6** Water Distribution Loop (Direct Feed System). Potential layout of a direct feed system for water purification in a dialysis center. Indirect feed systems (not shown) include a water storage tank.

Monitoring the Water Distribution Loop

- Flow velocity through the loop should be at least 3 ft/s for indirect systems and at least 1.5 ft/s in direct systems. Flow velocity is calculated using the following formula: $V = Q/A$, where V is the flow velocity, Q is the flow, and A is the cross-sectional area of the pipe.
- Flow rate should be measured at the end of the loop during peak usage.
- Regular flow rate measurements can be used to calculate flow velocity to ensure that the velocity is meeting requirements. Measurements should be documented for routine review.

Other Water Treatment Components

Backflow preventer: The initial component of the water treatment system consists of check valves that prevent water from moving backward from the water treatment system and into the plumbing of the building. This device is necessary to protect the plumbing of the building from contamination in the event of sudden loss of water pressure.

Temperature-blending valve: Decreasing temperature will increase the viscosity of water, which can have an effect on the efficiency of the RO membrane in the water treatment system. Temperature-blending valves can be used to maintain feed-water temperature that is ideal for membrane performance. As an example, some RO membranes are rated for a temperature of 77°F, and the temperature-blending valve may be set between 60°F and 85°F to achieve best performance. The temperature-blending valve is more crucial in northern climates in the winter when dropping temperature may lead to the inability of RO to keep up with water demand. When temperature-blending valves fail, water temperature can rise quickly. Water temperature should be monitored and recorded at least daily when using temperature-blending valves. Trends in temperature fluctuation can indicate a failing valve.

Acid feed system: Water treatment components such as the RO and chlorine tanks function best at a pH of 7–8. Source water pH greater than 8.5 can be corrected with an acid feed system by adding inorganic acid to lower the pH. Conversely, systems to alkalinize the water can be added in cases where the pH is too low. Typically, acidic water is not a problem because water municipalities will alkalinize the water to protect metal plumbing systems. When using acid feed systems, pH should be monitored with an on-line continuous monitor fitted with an alarm or tested at least daily if using test strips. The measured pH should be between 7 and 8.

Booster pumps: Booster pumps are often needed to maintain pressure and flow velocity throughout the system. Booster pumps are controlled by pressure or flow switches and activate when water pressure or flow drops below a set level. If city water pressure is not high enough, a booster pump may be required to feed the RO. Booster pumps should be monitored periodically to ensure that they are turning on and off at the appropriate pressures or flow rates.

Drain system: The drainage system must be capable of supporting maximal flow from all water treatment system components and should have an air break or some other means to prevent backflow of sewer water into the treatment system should there be an obstruction to flow in the sewer main. Drain systems can sometimes become malodorous. Acetate in spent dialysate can attract fruit flies. Treating the drain line with bleach can be an effective remedy.

Monitoring for Microbiologic Contamination

Water treatment systems for hemodialysis are under the constant threat of microbial contamination. Testing for bacteria and endotoxin in the water treatment system should take place at least monthly. Crucial components of the water treatment system, such as the first station in the loop, the last station in the loop, the RO, and storage tanks, should be tested monthly. During times of contamination, when testing standards are not met, testing frequency should increase too at least weekly. Each dialysis station in the loop should be sampled at least once annually. Samples should be collected just before scheduled disinfection and no sooner than 24 hours after disinfection. Samples from the loop should be collected in a "clean catch" manner after allowing the sample port to be rinsed for 1 minute. Loop sample ports should not be disinfected prior to sampling. Around 50 mL placed in a sterile endotoxin-free container is usually necessary. Dialysate from each dialysis machine should be collected at least annually, with at least two machines sampled every month. Dialysate samples are drawn from a sample port in the dialysate line, which can be sterilized with alcohol. It is also allowed to dry prior to placing a sterile syringe on the sample port and extracting 30 mL of dialysate for testing.

Special culture media should be used by the lab that is conducive to the growth of fastidious water-borne organisms (tryptone glucose extract agar or Reasoner's agar). Endotoxin levels are measured using the limulus amebocyte lysate (LAL) assay. Methods used by the laboratory for culture count and endotoxin levels should be appropriately validated. All testing results should be recorded on a log sheet and trends analyzed regularly, in the context of the loop design, to identify and locate any problems that may exist with contamination of the water treatment components.

Bacteria and endotoxin levels should not exceed values listed in Table 7.6. If the action level is reached, the dialysis unit should have a plan in place to address the contamination, and subsequent testing should follow to ensure that the plan is effective. Corrective action for positive culture counts or high endotoxin levels can include:

- Increasing the frequency of water testing
- Increasing the number of sites tested
- Disinfection and cleaning of the RO
- Loop disinfection
- Increasing the frequency of disinfection
- Installing an endotoxin retentive filter
- Confirming that endotoxin retentive filters are not failing or contaminated

TABLE 7.6 Recommended Maximum Allowable Levels for Total Viable Microbial Count (TVC, Also Known as Colony Count) and Endotoxins in Dialysis Water

	Maximum Allowable Level	Action Level	Ultrapure Dialysate
TVC	<100 CFU/mL	50 CFU/mL	<0.1 CFU/mL
Endotoxin	<0.25 EU/mL	0.125 EU/mL	<0.03 EU/mL

ISO 13959, AAMI 2011.

- Confirming that no dead spots exist in the loop plumbing
- Confirming that the water supply line connecting the machine to the loop is properly disinfected during loop disinfection
- Ensuring that proper disinfection procedures are followed

Routine disinfection of the water treatment system must be performed at a minimum every month. Monthly disinfection of the loop should include disinfection of the machine supply lines that are not routinely disinfected during the machine disinfection cycle. Water treatment systems can be heat sterilized, or chemicals such as sodium hypochlorite, peroxide, or formaldehyde can be used. If chemical disinfection is utilized, after the water treatment system is disinfected and rinsed, the water must be tested for residual chemicals. The disinfection process and testing should be clearly and completely documented and reviewed monthly.

Recommended Readings

Azar A, Ahmad S. Hemodialysis water treatment system. In: *Modelling and Control of Dialysis Systems.* Berlin: Springer-Verlag; 2013:347–378.

Book chapter published that provides a nice overview of the different water contaminants, different methods of water purification, and a technical review of the components of a water treatment system.

CMS Conditions for Coverage. <http://www.cms.gov/Regulations-and-Guidance/Legislation/CFCsAndCoPs/ESRD.html>.

The Conditions for Coverage reviews expectations from the Centers for Medicare and Medicaid Services (CMS) of dialysis providers. Included in the conditions for coverage are regulations related to water treatment standards for dialysis providers. Governmental regulations tend to lag behind the latest ISO recommendations. The most recent release of the Conditions for Coverage was in 2008.

CMS ESRD Interpretative Guidance. <https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/downloads/SCletter09-01.pdf>.

A memorandum from the Centers for Medicare and Medicaid Services (CMS) to state surveyors of dialysis units that provides some guidance on how to interpret the conditions for coverage. Pages 33–110 contain useful information for dialysis providers regarding water and dialysate preparation.

Coulliette AD, Arduino MJ. Hemodialysis and water quality. *Semin Dial.* 2013;26(4):427–438.

Review of water purification methods. Provides a nice compilation of case reports published that detail failures of water treatment components and how patients have been adversely affected when the water treatment system fails.

Fendley DA, Ward RA. Dialysate quality: new standards require a new approach to compliance. *Semin Dial.* 2012;25(5):510–515.

Journal article that highlights the latest water quality standards and considerations that should be taken into account when monitoring the dialysis water treatment system. Updated culture methods and lower thresholds for colony count and endotoxin levels are highlighted.

Glorieux G, Neirynck N, Veys N, Vanholder R. Dialysis water and fluid purity: more than endotoxin. *Nephrol Dial Transplant.* 2012;27(11):4010–4021.

Review of the limitations of current methods for monitoring water for microbiologic purity. Provides some context to where the future of water monitoring may be headed. Importance of water fluid purity in the era of increasing use of on-line generation of replacement fluid for the provision of hemodiafiltration is appreciated.

Guidance for the preparation and quality management of fluids for hemodialysis and related therapies. ANSI/AAMI/ISO 23500:2011.

Covers the appropriate preparation of dialysate, including handling of concentrates, operation of water treatment equipment and handling of its product water, monitoring of systems and the dialysate produced in settings such as in-center outpatient dialysis, acute inpatient dialysis, and home dialysis. Presents a quality management approach to ensuring routine production of dialysate meeting appropriate fluid quality standards.

NW Renal Network. EBCT and flow velocity calculators. <www.nwrenalnetwork.org/WaterTreatmentCalculator.xls>.

A spreadsheet calculator released by ESRD network 16 that is useful for the calculation of EBCT and for the calculation of flow velocity in English units of measurement.

NW Renal Network. Monitoring your dialysis water treatment system. <http://www.nwrenalnetwork.org/watermanual.pdf>.

A document released by ESRD Network 16 that covers the northwest portion of the United States, this manual provides some useful information to dialysis facility technicians and clinicians about how to monitor water treatment systems.

8

Dialysate Composition

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Introduction

Patients with end-stage kidney disease (ESKD) depend on dialysis to maintain fluid and electrolyte balance. In hemodialysis, solutes diffuse between blood and dialysate such that, over the course of the procedure, plasma composition is restored toward normal values. The makeup of the dialysate is of paramount importance in accomplishing this goal. Individualizing the dialysate composition is of critical importance in improving tolerance to the procedure, particularly given the number of comorbid conditions typically found in ESKD patients.

Dialysate Sodium

As dialysis has evolved, there has been continued interest in adjusting the dialysate sodium (Na^+) concentration in an attempt to improve the tolerability of the procedure. In the early days of dialysis, fluid removal was accomplished by a process of osmotic ultrafiltration. High concentrations of glucose were placed in the dialysate in order to create an osmotic driving force for fluid removal since the coil dialyzers used at the time were unable to withstand high transmembrane hydrostatic pressures. In order to prevent the development of hypernatremia as water moved from plasma to dialysate, the Na^+ concentration in dialysate was purposely set low, usually in the range of 125–130 mEq/L. With the development of more resilient membranes capable of withstanding high transmembrane pressures, osmotic ultrafiltration was replaced by hydrostatic ultrafiltration. Initially, a low dialysate Na^+ concentration continued to be used in order to avoid the problems of chronic volume overload, such as hypertension and heart failure. With the institution of shorter treatment times, volume removal became more rapid, and symptomatic hypotension emerged as a common and often disabling problem during dialysis. It soon became apparent that changes in the serum Na^+ concentration, and more specifically changes in serum osmolality, were playing a role in the development of this hemodynamic instability.

The importance of a stable plasma osmolality in maintaining hemodynamic stability was first suggested when the hemodynamic profiles of ultrafiltration were compared to diffusional solute clearance. Ultrafiltration alone (the removal of isoosmolar fluid by exerting a transmembrane pressure across the dialyzer) decreases cardiac output primarily due to a reduction in the stroke volume but is accompanied by an increase in peripheral vascular resistance such that arterial pressure is maintained. By contrast, diffusional dialysis results in a fall in arterial pressure while peripheral vascular resistance remains the same. With conventional dialysis (ultrafiltration and dialysis), less volume removal can be achieved before hypotension occurs as compared to ultrafiltration alone.

In animal studies, both conventional dialysis and sequential ultrafiltration dialysis result in an ultrafiltrate volume that is less than the decrease in extracellular fluid volume, consistent with a shift of fluid into the intracellular compartment. In addition, during sequential ultrafiltration hemodialysis, this shift occurs only during the diffusive phase. In the initial period of dialysis, the extracellular urea concentration rapidly falls, creating an osmotic driving force for water movement into cells due to the higher intracellular urea concentration. With the advent of high-clearance dialyzers and more efficient dialysis techniques, this decline in plasma osmolality becomes more apparent as solute is more rapidly removed. Use of a low dialysate Na^+ concentration tends to further augment the intracellular shift of fluid further as plasma tends to become even more hypoosmolar, consequent to the movement of Na^+ from plasma to dialysate.

Raising dialysate Na^+ to between 139 and 144 mEq/L improves hemodynamic stability and general tolerance to the procedure. A high dialysate Na^+ concentration has been shown to be effective in maintaining a relatively constant plasma osmolality, thereby minimizing intracellular water movement during dialysis. By preventing a decrease in plasma osmolality, the higher Na^+ dialysate leads to mobilization of fluid from the intracellular space, resulting in better preservation of plasma volume. As the dialysate to plasma Na^+ gradient increases, there is a greater contraction of the intracellular fluid compartment. The shift of fluid into the extracellular fluid space increases the hydrostatic pressure of the interstitium, which in turn favors refilling of the vascular space during volume removal. The net effect is a reduced frequency of hypotension and cramps.

The primary concern with use of a higher dialysate Na^+ concentration is the potential to stimulate thirst and cause increased weight gain and poor blood pressure control in the interdialytic period. Studies addressing this issue confirmed that a higher dialysate Na^+ modestly increased interdialytic weight gain. However, this excess weight was found to be readily removed with improved tolerance to ultrafiltration.

Sodium modeling refers to a strategy of varying the concentration of Na^+ in the dialysate during the procedure so as to minimize the potential complications of a high Na^+ solution while retaining the beneficial hemodynamic effects. A high dialysate Na^+ concentration is used initially with a progressive reduction toward isotonic or hypotonic levels by the end of the procedure. This method allows for a diffusive Na^+ influx early in the session to prevent the rapid decline in plasma osmolality resulting from the efflux of urea and other small molecular weight solutes. During the remainder of the procedure, when the reduction in osmolality accompanying urea removal is less abrupt, the lower dialysate Na^+ level minimizes the development of hypertonicity and potential for excess thirst, fluid gain, and worsening of hypertension in the interdialytic period. Unfortunately, despite the theoretical predictions of Na^+ modeling, the incidence of symptomatic hypotension during dialysis or the degree of interdialytic weight gain between fixed or variable Na^+ protocols have been difficult to demonstrate. In fact, the available data suggest that in most chronic dialysis patients, changing the dialysate Na^+ during the course of the treatment offers little advantage over a constant dialysate Na^+ of between 140 and 145 mEq/L.

In many of the comparative studies, the time-averaged concentration of Na^+ has been similar, potentially accounting for the inability to demonstrate a superiority of Na^+ modeling. For example, a linear decline in dialysate Na^+ from 150 to 140 mEq/L will produce approximately the same postdialysis plasma Na^+ as occurs when a fixed dialysate Na^+ of 145 mEq/L is used. In addition, the optimal time-averaged Na^+ concentration, whether administered in a modeling protocol or with a fixed dialysate concentration, is likely to vary from patient to patient as well as in the same patient during different treatment times. This variability is supported by studies demonstrating wide differences in the month-to-month predialysis Na^+ concentration in otherwise stable dialysis patients.

A special report authored by a coalition of dialysis organization leaders emphasizes the need to prevent intradialytic Na^+ overload by recommending that the dialysate Na^+ should be in the range of 134–138 mEq/L. To minimize the chance of hypotension and ensure adequate volume removal, the expected minimum duration of dialysis should be 4 hours in patients receiving thrice-weekly maintenance dialysis. Lastly, hypertonic saline and Na^+ modeling protocols should be avoided.

Despite these recommendations, there are certain situations where Na^+ modeling may be considered (Table 8.1). Patients initiating dialysis with marked azotemia are often deliberately dialyzed to decrease the urea concentration slowly over the course of several days to avoid the development of the dialysis disequilibrium syndrome. The use of a high/low-Na^+ dialysate in these patients may minimize fluid shifts into the intracellular compartment and decrease the tendency for neurologic complications. A modeling protocol may also be beneficial in patients suffering frequent intradialytic hypotension, cramping, nausea, vomiting, fatigue, or headache. In such patients, Na^+ modeling can be individually tailored to minimize increased thirst, weight gain, and hypertension. Combining dialysate Na^+ profiling with a varying rate of ultrafiltration may provide additional benefit in particularly symptomatic patients. This combined approach may be of particular benefit in ensuring hemodynamic stability in patients with acute kidney injury in the intensive care unit. Whenever prescribing a Na^+ gradient protocol, it is important to monitor the patient for evidence of a progressive increase in total body Na^+ manifesting itself as large interdialytic weight gains and/or uncontrolled hypertension (Table 8.2).

TABLE 8.1 Indications and Contraindications for Na^+ Modeling (High/Low Programs)

A. Indications (only use short-term and in highly selected patients, should generally be avoided)
- Intradialytic hypotension
- Cramping
- Initiation of hemodialysis in setting of severe azotemia
- Hemodynamically unstable patient (as in intensive care unit setting)

B. Contraindications
- Intradialytic development of hypertension
- Large interdialytic weight gain induced by high Na^+ dialysate
- Hypernatremia

TABLE 8.2 Factors Affecting K^+ Removal During Hemodialysis

A. Shifts K^+ into cell, thereby ↓ dialytic K^+ removal
- Exogenous insulin
- Glucose containing dialysate vs glucose-free dialysate
- β-adrenergic agonists
- Correction of metabolic acidosis during dialysis

B. Shifts K^+ to extracellular space or impairs K^+ uptake, increasing dialytic K^+ removal
- β-blockers
- α-adrenergic receptor stimulation
- Hypertonicity

Current research is focusing on ways in which the dialysate Na^+ concentration can be adjusted to more accurately match intradialytic Na^+ removal with interdialytic Na^+ intake. The ability to achieve zero Na^+ balance would enhance the ability to control hypertension in the interdialytic intervals and minimize the risk of hypotension during the dialysis procedure.

With the increased ability to individualize the dialysate Na^+ concentration, one can envision a scenario in which a patient initiated on hemodialysis is initially treated with a dialysate Na^+ concentration designed to achieve negative Na^+ balance. Once the patient becomes normotensive or requires minimal amounts of antihypertensive medications, the dialysate Na^+ can be adjusted on a continual basis to ensure that Na^+ balance is maintained. Identifying and delivering an individualized optimal dialysate Na^+ are unmet needs in kidney replacement therapy.

Dialysate Potassium

In most chronic outpatient dialysis centers, there is little individualization of the dialysate potassium (K^+) concentration. Rather, most patients are dialyzed with a K^+ bath that is prepared centrally and delivered with a concentration fixed at 1 or 2 mEq/L. When using a fixed dialysate K^+, it is difficult to predict the exact amount of K^+ that will be removed in a given dialysis session. Typically, one should not expect more than 80–100 mEq of K^+ removal even with the use of a K^+-free dialysate. In addition, there will be marked variability in the amount of K^+ removed from patient to patient despite similar predialysis K^+ levels and dialysis regimens. This variability is due to several patient-specific factors that influence K^+ shift from the intracellular to the extracellular space and ultimately into the dialysate.

The removal of excess K^+ by dialysis is achieved by use of a dialysate with a K^+ concentration lower than that of plasma, creating a gradient favoring K^+ removal; its rate is largely a function of this gradient. Plasma K^+ concentration falls rapidly in the early stages of dialysis, but as the plasma concentration falls, K^+ removal becomes less efficient. Movement of K^+ from the intracellular space to the extracellular space is the limiting factor in K^+ removal because K^+ is freely permeable across the dialysis membrane. Factors that importantly dictate the distribution of K^+ between these two spaces include changes in acid–base status, tonicity, glucose and insulin concentration, and catecholamine activity (Table 8.2).

The movement of K^+ between the intracellular and extracellular space is influenced by changes in acid–base balance that occur during the dialysis procedure. Extracellular alkalosis causes a shift of K^+ into cells, whereas acidosis results in K^+ efflux from cells. During a typical dialysis, there is a net addition of base to the extracellular space, which promotes cellular uptake of K^+ and, therefore, attenuates the removal of K^+ during dialysis. The degree to which K^+ shifts into the cell is directly correlated with the bicarbonate concentration of the dialysate. However, with routine dialysis, the change in blood pH is small in magnitude, and the effect on K^+ removal is not profound. By contrast, dialysis in patients who are acidotic will result in less K^+ removal because K^+ is shifted into cells as the serum bicarbonate rises.

Insulin is known to stimulate the cellular uptake of K^+ and can therefore influence the amount of K^+ removal during dialysis. The use of a glucose-free dialysate results in greater amounts of K^+ removal when compared with use of a glucose-containing bath. The use of a glucose-free dialysate results in lower levels of insulin. As a result, there is increased movement of K^+ to the extracellular space, where it becomes available for dialytic removal.

Changes in plasma tonicity can affect the distribution of K^+ between the intracellular and extracellular space. Administration of hypertonic saline or mannitol is sometimes used in the treatment of hypotension during dialysis. These agents would be expected to favor K^+ removal during dialysis because the resultant increased tonicity would favor K^+ movement into the extracellular space. There are no studies addressing whether there is any significant clinical benefit with this approach.

β-adrenergic stimulation shifts K^+ into cells and lowers the extracellular concentration. Inhaled β-adrenergic stimulants are effective in the acute treatment of hyperkalemia, so such therapy before dialysis may lower the total amount of K^+ removed during the dialytic procedure.

Alterations in serum K^+ concentration during dialysis can affect systemic hemodynamics. A decrease in serum K^+ concentration during hemodialysis would be predicted to increase systemic vascular resistance. Hypokalemia has been shown to increase resistance in skeletal muscle, skin, and coronary vascular beds, possibly through effects on the electrogenic Na^+/K^+-ATPase pump in the sarcolemmal membranes of vascular smooth muscle cells. In addition, decreased serum K^+ concentration may enhance the sensitivity of the vasculature to endogenous vasopressor hormones.

Changes in serum K^+ concentration during dialysis may also influence systemic hemodynamics through effects on myocardial performance. Dialysis is associated with an increase in contractility, which can be attributed to an increase in plasma ionized calcium concentration. Increased ionized calcium is most closely related to improved ventricular contractility, but modifying effects of concomitant decreases in K^+ may also be important.

An increase in peripheral vascular resistance secondary to the development of hypokalemia could have potentially detrimental effects on dialysis efficiency. This decrease in efficiency would result from decreased blood flow to urea-rich tissues such as skeletal muscle and, in effect, increase the amount of body-wide recirculation. Although more studies are needed in this area, it is likely that any effect of a low dialysate K^+ concentration to decrease dialysis adequacy is small in magnitude. In addition, increasing the dialysate K^+ concentration to improve dialysis adequacy will increase the risk of hyperkalemia during the interdialytic period.

Most patients dialyzed with a fixed K^+ dialysate tolerate the procedure well and do not suffer from complications of hypokalemia or hyperkalemia. Nevertheless, there are clinical conditions in which an individualized dialysate K^+ concentration may be useful. Patients with underlying heart disease, particularly in the setting of digoxin therapy, are prone to arrhythmias as hypokalemia develops toward the end of a typical treatment. The risk of arrhythmias is also increased in the early stages of a dialysis session when the plasma K^+ concentration may still be normal but rapidly declining. The sudden reduction in the plasma K^+ concentration during the initial portions of the dialysis procedure has been shown to unfavorably alter the QTc (a marker of risk of ventricular arrhythmias) even in dialysis patients without obvious heart disease.

Setting the dialysate K^+ concentration to a higher value in any patient at risk for arrhythmias is not without risk. In an analysis of more than 80,000 maintenance hemodialysis, predialysis serum K^+ values between 4.6 and 5.3 mEq/L were associated with the greatest survival, whereas values < 4.0 or ≥ 5.6 mEq/L were associated with increased mortality. Use of a higher dialysate K^+ concentration was associated with increased mortality in patients with predialysis K^+ values ≥ 5.0 mEq/L. A separate case-control study found the use of a low K^+ dialysate (< 2.0 mEq/L) as an independent risk factor for the specific occurrence of in-center sudden cardiac arrest. Patients with cardiac arrest who were on low K^+ dialysate were noted to have lower predialysis serum K^+ than the control patients on low K^+ dialysate. Taken together, when considering the risk for cardiac death or mortality, predialysis serum K^+ should help guide the decision of the dialysate K^+ with caution to avoid excessively high or low serum K^+ levels.

Modeling the dialysate K^+ concentration in such a way as to minimize the initial rapid decline in the plasma K^+ concentration may be one way to minimize potential cardiac toxicity. Exponentially lowering the dialysate K^+ during the course of the procedure to maintain a constant blood-to-dialysate K^+ gradient is one way to accomplish this goal. In addition to decreasing arrhythmias, maintenance of a constant blood-to-dialysate K^+ concentration may prove useful in patients who tend to develop worsening hypertension during the course of the dialysis procedure because of the effects of hypokalemia to cause increased vascular resistance, as mentioned previously. Lengthening dialysis treatment time or prescribing more frequent treatments using higher dialysate K^+ baths and/or lower blood and dialysate flow rates can also reduce the degree of K^+ shift but may be difficult to implement given logistical considerations. Prescribing K^+ binding agents to reduce predialysis hyperkalemia to allow use of a higher dialysate K^+ is an additional strategy to limit rapid lowering of K^+ during the initial part of treatment.

In summary, because of the kinetics of K^+ movement from the intracellular to the extracellular space, one can expect only up to 70–90 mEq of K^+ to be removed during a typical dialysis session. As a result, one should not overestimate the effectiveness of the dialytic procedure in the treatment of severe hyperkalemia. The total amount removed will exhibit considerable variability and will be influenced by changes in acid–base status, changes in tonicity, changes in glucose and insulin concentrations, and catecholamine activity. Studies examining the hemodynamic effect of K^+ fluxes during hemodialysis are limited. More importantly, deliberate alterations in dialysate K^+ concentration to affect hemodynamic stability would not be without risk. Use of low dialysate K^+ concentration may contribute to arrhythmias, especially in those patients with underlying coronary artery disease or those taking digoxin, and dialysate $K^+ < 2.0$ mEq/L should generally be avoided. On the other hand, use of dialysate with a high K^+ concentration may predispose patients to predialysis hyperkalemia. In patients who are at high risk for arrhythmias on dialysis, modeling the dialysate K^+ concentration to maintain a constant blood-to-dialysate K^+ gradient throughout the procedure may be of clinical benefit.

Dialysate Buffer

Bicarbonate is the principal buffer used in dialysate. Producing bicarbonate dialysate requires a specifically designed system that mixes a bicarbonate concentrate and an acid concentrate with purified water. The acid concentrate contains a small amount of either lactic or acetic acid and all the calcium and magnesium. The exclusion of these cations from the bicarbonate concentrate prevents the precipitation of magnesium and calcium carbonate that would otherwise occur in the setting of a high bicarbonate concentration. During the mixing procedure, the acid in the acid concentrate will react with an equimolar amount of bicarbonate to generate carbonic acid and carbon dioxide. The generation of carbon dioxide causes the pH of the final solution to fall to approximately 7.0–7.4. This more acidic pH, as well as the lower concentrations of calcium and magnesium in the final mixture, allow for these ions to remain in the solution. The final concentration of bicarbonate in the dialysate is generally fixed in the range of 33–38 mmol/L.

The use of a bicarbonate dialysate is associated with a number of potential complications. The liquid bicarbonate concentrate can be responsible for microbial contamination of the final dialysate, largely because the bicarbonate concentrate is an excellent bacterial growth medium. This complication can be minimized by short storage time as well as filtration of the concentrate during the production procedure. Use of a bicarbonate cartridge can further minimize this complication. This device allows for the bicarbonate concentrate to be produced online by passing water through a column containing powdered bicarbonate. The concentrate is produced and proportioned immediately before mixing with the acid concentrate. Hypoxemia may occur during bicarbonate dialysis when high concentrations of bicarbonate are used. This complication appears to be the result of suppressed ventilation secondary to the increase in pH and serum bicarbonate concentration. In addition,

excessively high levels of bicarbonate in the dialysate may result in acute metabolic alkalosis, causing mental confusion, lethargy, weakness, and cramps.

The factors that determine bicarbonate requirements in hemodialysis patients include acid production during the interdialytic period, the removal of organic anions during the hemodialysis procedure, and the buffer deficit of the body. Because these factors are likely to vary from patient to patient, there is increasing interest in individualizing the dialysate bicarbonate concentration (Table 8.3). The optimal level of dialysate bicarbonate is a concentration low enough to prevent significant alkalosis in the postdialytic period and yet high enough to prevent predialysis acidosis.

A low predialysis serum bicarbonate level may contribute to protein-energy wasting and greater intradialytic electrolyte shifts, thus leading to higher mortality. Higher bicarbonate dialysate concentration has been associated with improvement in nutritional markers, bone metabolism, as well as hemodynamic stability. A recent publication from the Dialysis Outcomes and Practice Patterns Study (DOPPS) found that a high dialysate bicarbonate concentration may be associated with increased morbidity and mortality, likely through adverse effects related to postdialysis metabolic alkalosis. However, a causal relationship could not be proven, given the observational design of the study.

The prescription of the dialysate bicarbonate is best tailored to the individual patient's acid–base status. Maintaining a predialysis total CO_2 concentration of at least 23 mEq/L is a reasonable goal. This can be achieved in most patients by individually adjusting the dialysate bicarbonate concentration. Substituting citric acid for acetic acid in the acid concentrate is also effective in improving the acidosis of chronic dialysis patients. Citric acid dialysate is associated with an increased delivered dose of dialysis, an effect postulated to be due to improved membrane permeability resulting from citrate's local anticoagulant effect. Improved membrane permeability with greater diffusive flux of bicarbonate from dialysate to blood or metabolism of citrate to

TABLE 8.3 Considerations When Individualizing Components of the Dialysate

Dialysate Component	Advantage	Disadvantage
Na^+: Increased	More hemodynamic stability	Dipsogenic effect
	Less cramping	Increased interdialytic weight gain
		Worsening of hypertension
Decreased	Less interdialytic weight gain	Intradialytic hypotension and cramping more common
Ca^{2+}: Increased	Suppression of PTH, promotes hemodynamic stability	Hypercalcemia with vitamin D and Ca^{2+}-containing phosphate binders
Decreased	Permits greater use of vitamin D and calcium-containing phosphate binders	Potential for negative calcium balance, stimulation of PTH, slight decrease in hemodynamic stability
K^+: Increased	Less arrhythmias in the setting of digoxin or coronary heart disease, less rebound hypertension	Limited by hyperkalemia
Decreased (ramped or modeling of dialysate K^+ ideal, can prevent rapid initial decline in plasma K^+)	Greater dietary intake of K^+ with less hyperkalemia	Increased arrhythmias, may exacerbate autonomic insufficiency
	? Improvement in myocardial contractility	
HCO_3: Increased	Corrects chronic acidosis, thereby benefiting nutrition and bone metabolism	Postdialysis metabolic alkalosis
Decreased	Less metabolic alkalosis	Potential for chronic acidosis
Mg^{2+}: Increased	? Less arrhythmias	Hypermagnesemia
	? Hemodynamic benefit	
Decreased	Permits use of Mg^{2+}-containing phosphate binders	Hypomagnesemia
PO_4 (rarely added to dialysate)	Treats or prevents hypophosphatemia in malnourished or chronic disease state, overdose setting, daily dialysis	Hyperphosphatemia

PTH, Parathyroid hormone.

bicarbonate in liver and muscle is the most likely explanation for the improvement in bicarbonate concentration.

The bicarbonate concentration used in most dialysis centers is set at 35 mmol/L and rarely adjusted. Given the evidence that correction of chronic acidosis is of clinical benefit, consideration should be given to adjusting the bicarbonate concentration with the goal of maintaining the predialysis tCO_2 concentration of > 22 mEq/L. In some patients, supplemental oral bicarbonate therapy will be required to achieve this goal. Substitution of citric acid for acetic acid in the acid concentrate is also a consideration. Further studies are needed to identify the optimal bicarbonate concentration for which hemodialysis patients experience the lowest rates of adverse clinical outcomes.

Dialysate Calcium

The calcium concentration in the dialysate can be varied extensively according to the individual needs of the patient. The most common concentrations used are 1.25, 1.5, and 1.75 mmol/L corresponding to 2.5, 3.0, and 3.5 mEq/L and 5.0, 6.0, and 7.0 mg/dL. In earlier times, a higher-end dialysate calcium concentration (typically 3.5 mEq/L) was widely used to provide a net flux of calcium into the patient. The substitution of calcium for aluminum-containing phosphate binders and the wider use of high doses of intravenous 1,25-$(OH)_2$-vitamin D made the likelihood of hypercalcemia more common, leading to a progressive lowering of the dialysate calcium concentration.

Despite the enthusiasm for use of low-calcium dialysate, studies have emphasized that such an approach requires careful monitoring to ensure that the patient does not develop negative calcium balance or worsening secondary hyperparathyroidism. In addition, a low-calcium dialysate can contribute to hemodynamic instability during the dialysis procedure. Raising the dialysate calcium concentration leads to an increase in ionized calcium concentration and an improvement in left ventricular contractility and less intradialytic hypotension. In patients prone to intradialytic hypotension who are at risk for hypercalcemia, dialysate calcium profiling can be used as a strategy to improve hemodynamic stability and yet minimize the potential for hypercalcemia.

Despite the favorable effects on hemodynamics, there is a concern that long-term use of a high dialysate calcium concentration may contribute to adverse effects on the cardiovascular system by promoting vascular calcification. A higher dialysate calcium concentration has been linked to progression of aortic calcification and increases in arterial stiffness. A final consideration in the selection of dialysate calcium is the rare occurrence of arrhythmias, including sudden cardiac death. One case-control study evaluating more than 43,000 prevalent hemodialysis patients over the course of 4 years identified low dialysate calcium (< 2.5 mEq/L) as an independent risk factor for the occurrence of in-clinic cardiac arrest. Further analysis established that a larger dialysate-to-plasma calcium gradient was linearly related to the risk for cardiac arrest. These retrospective studies should heighten the awareness that independent of bone and mineral disease, there are some risks involved with excessively low dialysate calcium.

In summary, the dialysate calcium concentration has implications with regard to metabolic bone disease, hemodynamic stability, and long-term effects on vascular calcification. The most recent National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) and Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend a dialysate calcium concentration of 1.25 and 1.25–1.5 mmol/L, respectively, as being a useful compromise between optimization of bone health and reductions in cardiovascular risk. However, as with the other dialysate constituents, the calcium concentration should be individually tailored to the patient. In patients who are prone to intradialytic hypotension, a higher dialysate calcium concentration may be of benefit. On the other hand, the use of a lower calcium concentration in the dialysate will allow increased doses of 1,25-$(OH)_2$-vitamin D to be used to reduce circulating levels of parathyroid hormone with less fear of inducing hypercalcemia. Further research is needed to define the optimal mix of dialysate calcium concentration, dose of vitamin D, amount of calcium- and non–calcium-containing phosphate binder, and use of the calcimimetic agents.

Dialysate Magnesium

The usual concentration of magnesium in the dialysate is 0.5–1.0 mEq/L and is only rarely manipulated. In an attempt to minimize the development of hypercalcemia associated with the use of calcium-containing phosphate binders and vitamin D, there has been some interest in using magnesium-containing compounds as a phosphate binder. Such a strategy requires a low dialysate magnesium concentration to avoid the development of hypermagnesemia. On the other hand, use of proton pump inhibitors can limit gastrointestinal absorption of magnesium and predispose to depletion. Monitoring of plasma magnesium is warranted in patients taking these drugs, especially in the setting of poor nutrition.

Dialysate Phosphate

In patients with mild to moderate hyperphosphatemia, hemodialysis has been estimated to remove 250–325 mg/day of phosphorus when extrapolated to an average week. Because a diet that provides adequate protein may provide approximately 900 mg of phosphorus daily, it follows that dialysis cannot provide adequate control of phosphate by itself. Rather, management of hyperphosphatemia requires a combination of dietary restriction, oral phosphate binders, and dialysis.

The limited ability of dialysis to remove phosphorus is primarily related to the kinetics of phosphorus distribution within the body and not inadequate clearance across the dialyzer. In a typical dialysis session, the rate of phosphorus removal is greatest during the initial stages of the procedure and then progressively declines to a constant low level toward the end of the treatment. This decline is due to the decrease in plasma concentration and the slow efflux of phosphorus from the intracellular space and/or mobilization from bone stores. Although dialysis membranes differ with respect to plasma clearance of phosphate, the slow transfer of phosphorus from the intracellular to the extracellular space where it becomes accessible for dialytic removal is the most important factor limiting phosphorus removal.

There are only a few situations where one might consider adding phosphorus to the dialysate. Hypophosphatemia can be an occasional finding in the chronic dialysis patient who is malnourished and suffering from some chronic disease state. In such patients, adding phosphorus to the dialysate may be an effective means to treat hypophosphatemia without having to use a parenteral route of administration. The phosphate must be added to the bicarbonate component of a dual proportioning system to avoid the precipitation of calcium phosphate that would result from the addition to the calcium-containing acid concentrate.

Another situation in which addition of phosphate to the dialysate may be useful is in the setting of an overdose. In a patient with normal kidney function and a normal serum phosphate concentration, use of a phosphate-free dialysate will commonly result in hypophosphatemia. In most circumstances, the hypophosphatemia is of short duration and is of little clinical consequence. However, some intoxications may increase the risk for complications of hypophosphatemia, such that addition of phosphate to the dialysate may be warranted.

Finally, hypophosphatemia is a potential complication in patients treated with prolonged daily nocturnal hemodialysis. In this setting, adding phosphate to the dialysate may prove useful as a means to normalize the serum phosphate concentration.

Recommended Reading

Alhosaini M, Leehey D. Magnesium and dialysis: the neglected cation. *Am J Kidney Dis.* 2015;66(3):523–531.

This is a comprehensive review of the factors related to measurement of plasma magnesium, magnesium balance, and the factors that affect magnesium flux during dialysis. Many factors affect plasma magnesium concentration, including diet, nutritional status (including plasma albumin level), medications (such as proton pump inhibitors), and dialysis prescription. The authors recommend that predialysis plasma magnesium be measured on a regular basis, with the dialysate magnesium concentration adjusted to maintain plasma magnesium concentration within the normal range..

Basile C, Pisano A, Lisi P, Rossi L, Lomonte C, Bolignano D. High versus low dialysate sodium concentration in chronic haemodialysis patients: a systematic review of 23 studies. *Nephrol Dial Transplant.* 2016 Apr;31(4):548–563.

The authors performed a systematic review of 23 studies and found inconclusive evidence to support either a low or a high Na+ dialysate in chronic hemodialysis patients. They argue for future studies examining the effects of altered dialysate Na+ on hard outcomes such as mortality.

Bressendorff I, Hansen D, Pasch A, et al. The effect of increasing dialysate magnesium on calciprotein particles, inflammation, and bone markers: post hoc analysis from a randomized controlled clinical trial. *Nephrol Dial Transplant.* 2021;36(4):713–721.

A single-center, randomized, controlled, double-blind trial comparing a standard dialysate magnesium of 0.5 mmol/L to a high dialysate magnesium of 1 mmol/L. The authors find the higher dialysate magnesium was associated with favorable changes in the capacity of serum to inhibit calcification.

Flythe J, Mc Causland F. Dialysate sodium: rationale for evolution over time. *Semin Dial.* 2017 Mar;30(2):99–111.

An excellent review of issues related to dialysate Na+.

Flythe J, Chang T, Gallagher M, et al. Conference participants blood pressure and volume management in dialysis: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. *Kidney Int.* 2020 May;97(5):861–876.

A summary of the KDIGO meeting providing consensus recommendations for blood pressure and volume management that include discussions of dialysate Na+.

Hung A, Hakim R. Dialysate and serum potassium in hemodialysis. *Am J Kidney Dis.* 2015;66(1):125–132.

The authors discuss the challenges regarding the safety of using a low-potassium dialysate given the concern about the effects that rapid and/or large changes in serum potassium concentrations may have on cardiac electrophysiology and arrhythmia. They discuss new approaches and practice standards for potassium removal during dialysis, as well as other modifiable triggers of sudden cardiac death, such as other electrolyte components of the dialysate (magnesium and calcium), rapid ultrafiltration rates, and safety of a number of medications.

Inrig JK. Intradialytic hypertension: a less-recognized cardiovascular complication of hemodialysis. *Am J Kidney Dis.* 2010;55:580–589.

This is a review of intradialytic hypertension and its association with adverse outcomes. The paper broadly covers the epidemiologic characteristics, prognostic significance, potential pathogenic mechanisms, prevention, and possible treatment of intradialytic hypertension. The author discusses the potential role of dialysate potassium and calcium in the genesis of this disorder.

Kovesdy C. Fluctuations in plasma potassium in patients on dialysis. *Nephrol Dial Transplant.* 2019 Dec 1;34(suppl 3):iii19–iii25.

The author discusses the fluctuations in potassium that occur in dialysis patients and how these changes may affect outcomes.

Palmer BF. Individualizing the dialysate in the hemodialysis patient. *Semin Dial.* 2001;14:41–49.

This is a comprehensive review of the components that make up the dialysate in hemodialysis and how these components can be individualized to the needs of patients.

Pun P, Horton J, Middleton J. Dialysate calcium concentration and the risk of sudden cardiac arrest in hemodialysis patients. *Clin J Am Soc Nephrol.* 2013;8:797–803.

This is a case-control study among 43,200 hemodialysis patients examining factors associated with sudden cardiac arrest occurrence. A low Ca^{2+} dialysate < 2.5 mEq/L, higher corrected serum Ca^{2+}, and increasing serum dialysate Ca^{2+} gradient were all found to be associated with increased risk of this complication.

Pun P, Lehrich R, Honeycutt E, Herzog C, Middleton J. Modifiable risk factors associated with sudden cardiac arrest within hemodialysis clinics. *Kidney Int.* 2011;79:218–227.

The authors identify dialysis-related factors associated with the increased risk of sudden death in a case-control study encompassing 43,200 patients dialyzed in outpatient clinics of a large organization. They identify a low dialysate potassium (less than 2 mEq/L) level as a major risk factor for this adverse outcome.

Pun PH, Middleton JP. Dialysate potassium, dialysate magnesium, and hemodialysis risk. *J Am Soc Nephrol.* 2017 Dec;28(12):3441–3451.

The authors provide an overview of factors affecting overall potassium balance and factors modulating potassium dialysate fluxes in dialysis and review data linking serum and dialysate potassium concentrations with arrhythmias, cardiovascular events, and mortality.

Severi S, Bolasco P, Badiali F, et al. Calcium profiling in hemodiafiltration: a new way to reduce the calcium overload risk without compromising cardiovascular stability. *Int J Artif Organs.* 2014;37:206–214.

A study demonstrating the utility of dialysate calcium profiling as a means to retain the advantages of high Ca^{2+} in terms of hemodynamic stability and modification of QTc while reducing the excessive positive calcium balance typical of dialysis with high Ca^{2+} content.

Sharma R, Rosner M. Glucose in the dialysate: historical perspective and possible implications? *Hemodial Int.* 2008;12:221–226.

This review examines the utility of glucose in the dialysate and discusses the potential implications on chronic inflammation in patients with ESKD. Although there is currently no evidence for a causal relationship between dialysate glucose concentration and the chronic inflammation seen in ESKD, this possibility is explored.

Tentori F, Karaboyas A, Robinson B, et al. Association of dialysate bicarbonate concentration with mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis.* 2013;62:738–746.

This is an observational study from the Dialysis Outcomes and Practice Patterns Study (DOPPS) examining the effects of dialysate bicarbonate concentration on all-cause and cause-specific mortality. The paper concludes that a high dialysate bicarbonate concentration may contribute to adverse outcomes, likely through the development of postdialysis metabolic alkalosis.

Weiner D, Brunelli S, Hunt A, et al. Improving clinical outcomes among hemodialysis patients: a proposal for a "volume first" approach from the chief medical officers of US dialysis providers. *Am J Kidney Dis.* 2014;64:685–695.

A special report from experts in the field arguing that normalization of extracellular fluid volume should be a primary goal of dialysis care. They emphasize the need to avoid intradialytic sodium loading by incorporating dialysate sodium concentrations set routinely in the range of 134–138 mEq/L, avoidance of routine use of sodium modeling, and avoidance of hypertonic saline solution.

9

Safety Monitors in Hemodialysis

JOANNE D. PITTARD, MS, RN

Hemodialysis monitors include machines, devices, protocols, and personnel. The major goal is to ensure patient safety during the hemodialysis procedure. All tasks that check, observe, keep track of, and control the hemodialysis treatment is monitoring procedures. These important tasks are too often lightly dismissed.

This chapter focuses on the fluid delivery system and extracorporeal circuit, their respective monitoring devices, functions, locations, performance standards, and management. Monitoring of the patient and hemodialysis prescription pre, during, and post dialysis are covered in other sections of this book. Incorporated are parts of the Conditions of Coverage (CfCs) dictated by the Department of Health and Human Services Center for Medicaid and Medicare Services (CMS), effective October 3, 2008, for end-stage renal disease (ESRD) facilities. The revised regulations update standards for delivering safe, high-quality care to dialysis patients. Specific regulations regarding dialysate (§494.40 Condition: Water and Dialysate Quality) remain unchanged. First-time regulations specific for dialysate include mixing, distribution, labeling, and use.

Definitions and Overview

The fluid delivery system is commonly called "the machine." The fluid delivery system prepares dialysate, a body temperature electrolyte solution. The dialysate flows through the dialysate compartment of the dialyzer, where dialysis occurs. A blood pump circulates the patient's blood through the extracorporeal circulation to the blood compartment of the dialyzer and back to the patient. The two major categories to monitor are the dialysate circuit and blood circuit.

The blood circuit consists of a blood tubing set (arterial and venous), blood side of the dialyzer, intravenous (IV) normal saline and administration line, and heparin syringe and infusion line.

The blood and dialysate are separate circuits that interface at the dialyzer membrane. The machine design must involve extensive monitoring of both circuits. Specific warning alarms must be initiated when the machine's preset limits are exceeded and/or an unsafe condition exists.

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Dialysate Solution

Dialysate solution or dialyzing fluid is a nonsterile aqueous electrolyte solution that is similar to the normal levels of electrolytes (Table 9.1) found in extracellular fluid, with the exception of the buffer bicarbonate and potassium. Dialysate solution is almost an isotonic solution, with the usual osmolality of approximately 300 ± 20 milliosmoles per liter (mOsm/L). To ensure patient safety and prevent red blood cell (RBC) destruction by hemolysis or crenation, the osmolality of dialysate must be close to the osmolality of plasma. The osmolality of plasma is 280 ± 20 mOsm/L. Dialysate solution commonly contains six electrolytes: sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), magnesium (Mg^{2+}), chloride (Cl^-), and bicarbonate (HCO_3^-). A s). A seventh component, the nonelectrolyte glucose or dextrose, is invariably present in the dialysate. The dialysate concentration of glucose is commonly between 100 and 200 mg/dL. Freshly prepared dialysate solution circulates continuously to the dialyzer in the extracorporeal circuit. After making a single pass through the dialyzer, the effluent dialysate goes to the drain.

Fluid Delivery System

The vast majority of dialysis facilities in the United States use single-patient fluid delivery systems. This type of equipment is self-contained, preparing the dialysate only for the individual machine. Some dialysis facilities use central delivery systems with central manufacture of dialysate. Although that system is more economical, it is less safe than the individual machines. The discussion will focus on single-patient machinery. A few safety issues unique to a central delivery system are explored as well.

Control Panel and Monitor Display

All modern fluid delivery systems have a frontal control panel (Fig. 9.1) by which pressure and other limits may be

TABLE 9.1 Comparison of Normal Blood Values and Dialysate Composition

Electrolyte	Dialysate Level Range	Normal Blood Value Range
Sodium	135–145 mEq/L	135–145 mEq/L
Potassium	0–4 mEq/L	3.5–5.5 mEq/L
Calcium	2.25–3.0 mEq/L	4.5–5.5 mEq/L
Magnesium	0.5–1.0 mEq/L	1.5–2.5 mEq/L
Chloride	100–115 mEq/L	95–105 mEq/L
Bicarbonate	30–40 mEq/L	22–28 mEq/L
Nonelectrolyte		
Dextrose	0–200 mg/dL	80–120 mg/dL

From Pittard J, De Palma J. *Dialysate Monograph*. 1st ed. Glendale, CA: Hemodialysis, Inc.; 2013.

set and system parameters may be viewed. The control panel and monitor display on the face of the machine will have audible and visual warning alarms as a mandatory part of safe dialysis monitoring.

Monitor Failure

Machine monitors are either mechanically or electrically operated, or a combination of both. All monitors can fail. Murphy's Law (if anything can go wrong, it will) should be remembered and accepted as fact. Murphy's Law is attributed to an engineer working at the Los Alamos laboratories in the 1950s. The truth of this statement can be reworded to, "If you can think of a possible disaster with the present equipment, take the necessary precautionary steps immediately, or it will happen." If one can access misadventure and incident reporting, virtually every possible projected failure of a monitor has occurred and has resulted in patient/staff injury or death.

Fail-Safe, a Misnomer

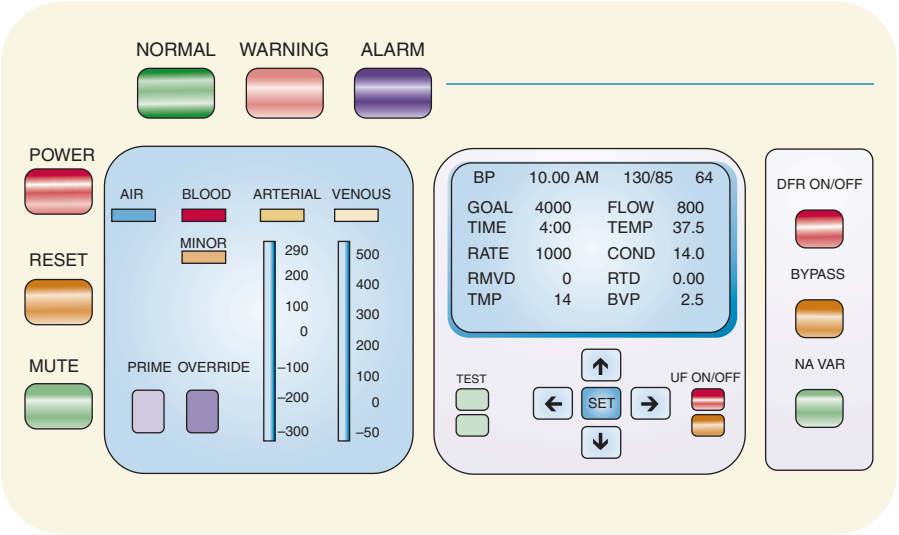
Machine monitors are frequently thought to be fail-safe devices, but they are not. A truly fail-safe device cannot be overridden to cause harm either by electronic or human intervention. By this narrow definition, there are no fail-safe dialysis machine monitors. Because all dialysis machine monitors can fail, they ought to be simple to operate and accurate—and should signal a warning when they are out of limits or not working properly. Any important factor requires dual monitoring: the machine monitor device and dialysis personnel. No machine, computer, or device can replace the continuous surveillance of the hemodialysis personnel.

Dialysate Circuit

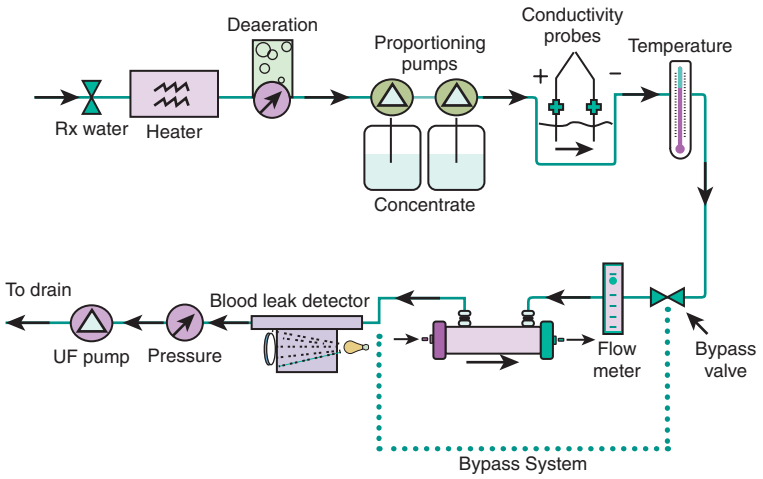
Fig. 9.2 displays components of the dialysate fluid path. Dialysate monitoring includes prescription, composition (conductivity and pH), temperature, flow, pressure, effluent, absence of impurities (cleaning and disinfecting agents), potential pyrogenic agents, and microbiologic testing. Each monitor or control is discussed in order of the usual flow of fluid, from the water inlet solenoid valve to the effluent dialysate drain line.

Why Discuss the Details of Dialysis Machinery?

Each dialysis treatment exposes the ESRD patient's blood to hundreds of liters of dialysate. The dialysate should be of pharmaceutical grade, as dialysate is the equivalent of an IV solution. The machinery that manufactures dialysate can



• **Fig. 9.1** Control Panel and Monitor Display. (From Pittard J. *Hemodialysis Nursing, Training Manual*. 7th ed, version 7.0. Santa Monica, CA; 2003, with permission.)



• **Fig. 9.2** Fluid Pathway Simplified. (From Pittard J. *Hemodialysis Nursing, Training Manual*. 7th ed, version 7.0. Santa Monica, CA; 2003, with permission.)

silently and quickly cause a patient serious injury or death because of contaminants or incorrect solute concentration. Even more distressing, if the machinery manufactures a substantially hypotonic fluid, but at a concentration that does not cause hemolysis, the patient may rapidly develop water intoxication, cerebral edema, seizures, and noncardiogenic pulmonary edema—signs and symptoms that the dialysis staff can easily misinterpret as requiring more ultrafiltration and more dialysis!

With current therapy using blood flow rates of 300 to 450 mL/min, the entire patient's circulating blood may be exposed to toxic chemicals or a hemolytic state in less than 15 minutes. Death can be both swift and the cause undiagnosed, even with postmortem examination. Each component of the dialysate circuit discussed, if it malfunctions, may induce hemolysis.

Water Inlet Solenoid

The water inlet solenoid permits the flow of treated water into the dialysis machine when the main power switch is activated and stops the flow when the main power is turned off. Treated water enters the machine via a water inlet valve with water pressure usually between 20 and 105 pounds per square inch (psi). The treated water for hemodialysis must meet the Association for the Advancement of Medical Instrumentation (AAMI) standards. Not all machines have a water inlet solenoid. Allowing water to flow into the machine without activating the machine's main power switch can cause problems with bacterial buildup in that portion of the fluid pathway.

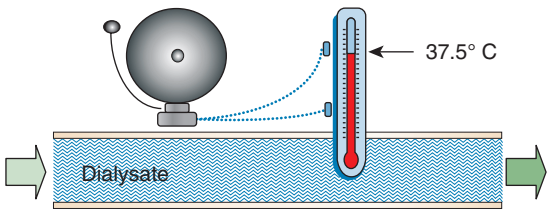
Solenoid Monitoring

The inlet water pressure can be measured using a dial-type manometer. This mechanism may malfunction or leak in the on or off position. There are neither published performance standards nor standard alarms for this device. Many machines have a continuous audible warning alarm to alert the staff of problems. If an alarm condition exists that indicates inadequate water flow or pressure, its role may be to prevent water from being overheated by the water heater. Overheated dialysate causes gross hemolysis.

Dialysate Temperature

A heater raises the temperature of the incoming water to approximately body temperature. Heating partially degasses the cold water, which improves the mixing of water and dialysate concentrate. A thermistor feedback circuit usually controls the electrical heating elements. The heater may have a coarse adjustment control inside the machine and a fine adjustment control on the front panel. There may be a simple bimetallic dial thermometer within some machines that, though not alarmed, provides visual observation of its function.

The dialysate temperature is usually maintained between 37°C and 38°C (98.6°F and 100.4°F) throughout the dialysis treatment although recent research has suggested that somewhat lower dialysate temperature, as tolerated, may be beneficial and better maintain intradialytic cardiovascular stability. An internal temperature sensor (Fig. 9.3) monitors the dialysate temperature continuously. In some cases, the actual temperature reading is displayed on the front panel of the machine. Other machines have lights on the front panel that indicates an alarm condition. Most fluid-delivery



• **Fig. 9.3** Dialysate Temperature. (From Pittard J. *Hemodialysis Nursing, Training Manual*. 7th ed, version 7.0. Santa Monica, CA; 2003, with permission.)

machines have high- and low-temperature monitor alarms. Some older-model machines have only high-temperature alarms. If the high or low internal temperatures exceed the preset internal limits, three actions result: an audible alarm, a visual alarm, and activation of the bypass mode.

Heater and Temperature Monitoring

Internal, factory-set, controls should limit dialysate temperature to between 33°C (92°F) and 39°C (102°F). The fine adjustment control knob on the front panel of the machine should not be capable of overriding this setting.

Temperatures Greater Than 106°F

The usual causes of high dialysate temperature are either a malfunctioning water heater with a temperature controller or a water flow restriction. The high internal limit should be set no higher than 41°C (105.8°F). Normal RBCs begin to hemolyze at 42°C. Overheated dialysate has been known to precipitate cardiac arrhythmias.

Although it is true that the efficiency of diffusion during dialysis is increased with increased dialysate temperature, without excellent electronic temperature monitoring, this is a dangerous way to increase dialysis efficiency. Under no circumstances should the high limit be adjusted above 41°C. Several articles in the literature suggest that the upper limits be set at 42°C (107.6°F), which is probably too high and may cause hemolysis. It should be remembered that uremic RBCs are more osmotically fragile and have a shorter half-life than normal RBCs. It is reasonable to assume that these uremic RBCs are more sensitive to all mechanical and thermal causes of trauma than normal RBCs.

Temperatures Less Than 98.6°F

Some nephrologists use lower-temperature dialysate in the belief that this promotes a more stable blood pressure response to high ultrafiltration. If low-temperature dialysate is used, the total dialysis time needs to be increased by about 8% for every 3°C below 98.6°F, as that is the theoretical loss in diffusivity with temperature decrease. Low dialysate temperatures may induce venous vessel spasms and make it impossible to obtain maximum blood flows through the artificial kidney.

With dialysate temperatures below 98.6°F, patients may complain of being cold, ask for a blanket, and some will actually shiver in an attempt to increase their core body temperature. An increase in cardiac irritability in patients with coronary vessel disease may be observed if temperatures are too low.

Deaeration System

The deaeration system removes dissolved gases by exposing water to subatmospheric pressures generated by a vacuum pump. The gases coalesce, form bubbles, and are vented to the atmosphere by a bubble trap. Improper or inadequate removal of dissolved gases in dialysate can be a hidden cause of several serious dialysis problems, including false blood-leak alarms, false conductivity alarms, interference with volumetric control function, and decreased dialysis efficiency by air bubbles trapped on the dialyzer membrane that reduces functional dialyzer surface area. Microbubbles streaming from dialysate into blood have been reported to collect in the right atrium of the heart and cause air embolism without triggering an air-foam detector alarm. Exaggerated frothing and blood clotting in the drip bulb chamber with minute blood clots being carried to the right atrium may also be seen. A substantial number of all adults have a potentially patent foramen ovale. If the pulmonary artery pressure increases, the foramen ovale can shunt blood from the right to the left atrium. This can result in a transfer of these small clots into the left heart and result in cerebral embolism. This set of conditions has occurred and is known as paradoxical embolism, which can be misdiagnosed as a transient ischemic attack (TIA) or other vascular insult and not embolic phenomenon.

Deaeration System Monitoring

Frequent false blood-leak alarms or rapid fluctuations in conductivity can indicate a malfunction of the vacuum pump. The machine should be removed from service and undergo maintenance. If the dialysate inflow and/or outflow lines are not correctly attached to the dialyzer, air can be pulled into the system. Proper technique by the dialysis staff who set up the dialysis machinery prior to dialysis and who secure the quick disconnects of the dialysate lines on the dialyzer dialysate ports will prevent this problem.

Mixing Device

The mixing device, also known as the proportioning system, proportions treated water and dialysate concentrate to create dialysate of the correct ionic concentration. The proportioning system ratio depends on the type of dialysate concentrate used and the type of fluid delivery system. Typical mixing ratios of water to dialysate concentrate are

- 34:1 or 44:1 for acid concentrate
- 20:1 or 25:1 for bicarbonate concentrate

The supply of treated water and dialysate concentrate generates dialysate flow rates between 500 and 1000 mL/min. The two basic types of proportioning systems are fixed-ratio mixing and servo-controlled mixing.

Fixed-ratio mixing uses diaphragms or piston pumps to deliver a set volume of water and concentrate to the mixing chamber. Servo-controlled mechanisms continuously monitor the dialysate composition with conductivity sensors that adjust the amount of concentrate mixed with water to maintain a variable or set composition.

In machines that add concentrate by a servo-controlled mechanism until the dialysate reaches a desired conductivity, a second independent conductivity and pH monitor must cause an alarm if the conductivity is incorrect. If acid and bicarbonate inputs are reversed, or if the wrong concentrates are used for a bicarbonate machine, the servo loops may make a solution of acceptable ionic strength (correct

conductivity) but of lethal ionic composition. In this case, the pH monitor or concentrate pump speed monitor becomes critical. However, not all machines are equipped with pH monitors, and this deadly event will not be diagnosed.

Mixing Device Monitoring

The conductivity and pH monitor will verify proper mixing with a fixed-ratio proportioning system. Equipment using servo-controlled mechanisms requires a diligent and trained staff to ensure that the proper dialysate concentrate is attached to the proper concentrate lines on the machine.

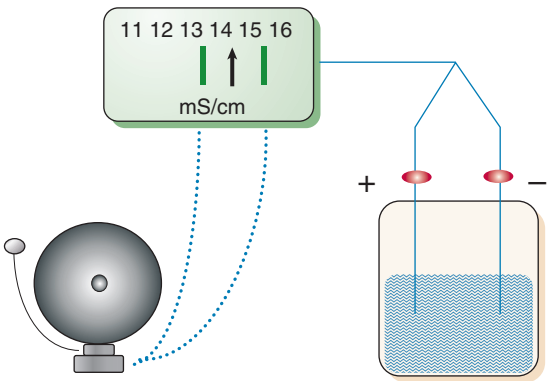
Composition and Conductivity of Dialysate

Analysis of the dialysate for the proper composition is necessary after it has been mixed, and prior to exposing it to the dialyzer and patient. All modern fluid delivery systems have conductivity cells and meters. Total conductivity of dialysate is measured as a simple assessment and surrogate for dialysate ionic content. A conductivity cell is connected to a meter that displays the total ionic concentration of dialysate. Conductivity cells should be made of high-quality, corrosion-resistant materials. The conductivity of an electrolyte solution increases as the temperature increases. Conductivity cells used to monitor dialysate must be temperature compensated.

Measuring Conductivity

In dialysis, conductivity is usually measured using a two-electrode system. The electrodes are connected to a constant current and an ammeter (Fig. 9.4). An electric current is passed through the solution between the electrodes. The ammeter measures the flow of current (the inverse of electrical resistance) that passes through the solution between the electrodes. The conductivity measurement is an estimate of the total ionic content of the dialysate and does not measure or reflect specific ions or electrolytes.

The conductivity meters read the conductivity in millimhos per centimeter (mmhos/cm) or milliSiemens per centimeter (mS/cm). A range of 12.5–16.0 mS/cm is acceptable for a standard dialysate solution. Some facilities prefer a tighter range, 13.0–15.5 mS/cm. The range varies slightly from facility to facility, depending on the dialysate formula in use.



• **Fig. 9.4** Conductivity Monitor. (From Pittard J. *Hemodialysis Nursing, Training Manual*. 7th ed, version 7.0. Santa Monica, CA; 2003, with permission.)

Monitoring Conductivity

Conductivity meters on dialysis machines have external and internal limits set. Some machines may have three internal conductivity sensors set at different intervals of control. The conductivity, or dialysate ionic composition, is so important that this monitoring redundancy is a commonsense safeguard against single-monitor failure. The closest tolerance internal high-low limits are set at ±5%; the last set of conductivity monitoring may be set at 50% of normal conductivity. If the first two monitors fail, the patient, without any alarms being triggered, will receive a massive infusion of hypotonic dialysate. Because different mixtures of ions have different conductivities, it is mandatory that the dialysate formulas determine the established conductivity setting.

It is now mandatory to perform and document an independent conductivity test prior to preparing the dialyzer for patient use and before the dialysis treatment is initiated. There are several methods available to perform an independent analysis of the machine's conductivity. The most common method is to use a portable conductivity meter that measures the total conductivity. Laboratory analysis that measures each electrolyte level can also be done.

When using independent analysis, be sure the reference conductivity meter is calibrated accurately prior to use. All standard solutions should be fresh and render acceptable readings.

If independent verification of the dialysate conductivity does not validate the conductivity meter, do not dialyze the patient with that machinery. A complete resolution of the problem is necessary before dialysis. Failure to resolve a problem prior to dialysis will only invite a potential disaster. It is best to bring in another dialysis machine and start over.

All facilities must have an established acceptable conductivity range, and this range must be publicly posted. Any deviation in the conductivity limits set should cause a conductivity alarm. A conductivity alarm causes three actions on the dialysis machine: an audible alarm, a visual alarm, and activation of the bypass system.

The bypass system diverts the dialysate to the drain before it can enter the dialysate inflow line leading to the dialyzer. Thus, exposure of the patient's blood in the dialyzer to an incorrect or unsafe dialysate composition is avoided.

No Intradialytic Conductivity Adjustments

Only a qualified and trained machine technician should adjust the external or internal conductivity limits. Under no circumstances should they be adjusted during the dialysis treatment. They must be properly adjusted and preset before the dialysis treatment. Serious and fatal accidents have occurred as a result of improper adjustments of the conductivity limits.

Low Conductivity

A low-conductivity alarm is the most common type of conductivity alarm (Fig. 9.5). The usual cause is a lack of concentrate in one or both acid and bicarbonate concentrate containers. Rarely, a low-conductivity alarm is due to incorrect dialysate concentrate.

If the internal or external low-conductivity limits are not adjusted properly and/or the machine does not go into the bypass mode, the patient's blood is exposed to hypotonic dialysate. Exposure to hypotonic dialysate can be fatal within a few minutes. Hypotonic dialysate causes a hypoosmolar state, and even without acute hemolysis, water intoxication can occur, which can also be lethal.

Low-Conductivity Monitoring

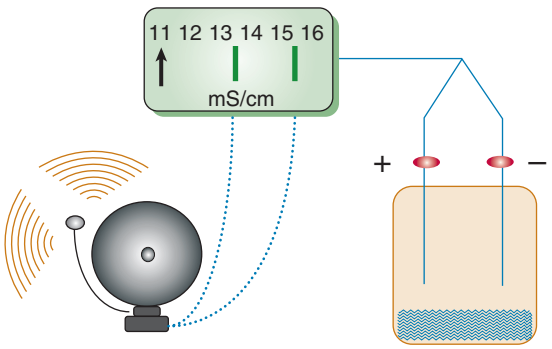
There must be an adequate amount of dialysate concentrate in the container(s) before starting dialysis. Dialysis staff should not rely on the conductivity meter to monitor dialysate concentrate supplies.

True, if the dialysis machine goes into bypass mode, there is no harm to the patient. But, when the dialysis machine is in the bypass mode, no dialysis is taking place and the time lost on dialysis is rarely, if ever, made up with a longer dialysis time the next dialysis session. If one accepts that the average dialysis in the United States comprises not the maximal amount of dialysis time, but probably the minimal amount of dialysis time, placing the dialysis machinery in bypass routinely will shorten the patient's life span.

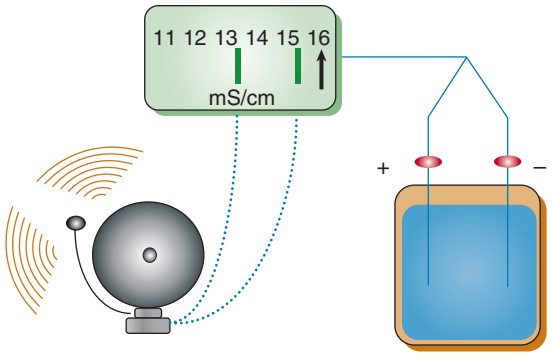
Most new model fluid-delivery machines have timers that stop with a dialysate circuit alarm. This ensures that the patient receives their allocated time on dialysis.

High Conductivity

High-conductivity alarms (Fig. 9.6) can result from inadequate water flow to the proportioning system, untreated incoming water with an excess of calcium, or incorrect hook-up of dialysate concentrate to the dialysis machine (if using servo-controlled mechanisms) and sodium modeling. Newer-model fluid delivery systems will not go into conductivity with incorrect hook-ups.



• **Fig. 9.5** Low-Conductivity Alarm. (From Pittard J. *Hemodialysis Nursing, Training Manual*. 7th ed, version 7.0. Santa Monica, CA; 2003, with permission.)



• **Fig. 9.6** High-Conductivity Alarm. (From Pittard J. *Hemodialysis Nursing, Training Manual*. 7th ed, version 7.0. Santa Monica, CA; 2003, with permission.)

With older machines, a common, serious cause of high conductivity occurs when two acid concentrate containers are connected to the dialysis machine instead of one acid container to the acid port and one bicarbonate container to the bicarbonate port. If the dialysis machine goes into bypass mode, there is no harm to the patient. However, if the internal or external high-conductivity limits have not been set correctly, the patient's blood is exposed to hypertonic dialysate and possibly hyperosmolar coma.

New model fluid-delivery systems have anautomatic built-in adjustment of conductivity limits for sodium variation, which causes an increase in conductivity. If sodium variation is done incorrectly, the patient will leave the dialysis thirsty, in a hyperosmolar state, and attempt to relieve that thirst with free water. This will result in a marked expansion of their extracellular volume (ECV), and possibly malignant hypertension.

High-Conductivity Monitoring

If a conductivity alarm occurs during the dialysis treatment, the bypass mode is activated. While correcting the alarm condition, the dialysis staff must not adjust the external or internal conductivity limits. Adjusting the conductivity limits during an alarm condition overrides the bypass mode and endangers the patient's life. If the alarm situation cannot be corrected, the treatment must be stopped, and the patient moved to another dialysis machine.

Acid–Base (pH) Control

Newer-model fluid-delivery systems will not go into conductivity if the pH is too high or too low. However, the majority of dialysis clinics perform independent pH tests before each dialysis. Fluid delivery machines using bicarbonate dialysate may or may not have pH monitors. There may be a pH meter on the front panel dialysis display with lights that activate when an alarm condition occurs.

Monitoring Acid–Base (pH)

The pH of dialysate is commonly checked by use of a pH paper test strip or bicarbonate pH test strips. With the pH paper test strips, the color change of the dialysate-soaked

test strip is compared with a list of colors for various pH values. The bicarbonate pH test strips interpret the results by comparing the indicator pad to the color chart on the bottle label. Acceptable range for test results is a pH of 7.5 ± 0.5 (7.0–8.0). If the pH is below or above the acceptable limits and the conductivity meter is within acceptable limits, the dialysis should not be carried out. Both the pH and conductivity must be within acceptable limits before initiating dialysis.

Bypass System

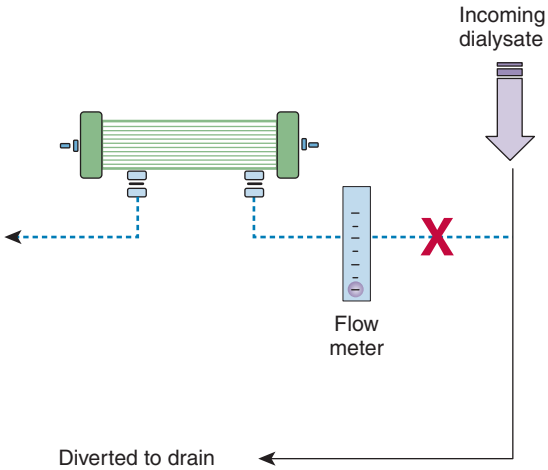
The bypass system diverts dialysate (Fig. 9.7) directly to the drain away from the dialyzer to avoid exposure of the patient's blood to unsafe dialysate. The dialysate bypass valve, located in the incoming dialysate circuit predialyzer, is activated by high/low conductivity, high/low pH, or high/low temperature. It is imperative to have the dialysis staff verify and check that the bypass valve diverts the dialysate to drain.

Bypass System Monitoring

There is no monitor for bypass system failure or function on most machines. A light on the front panel of the machine indicates when the machine is in the bypass mode. Also, an audible alarm usually occurs. If there is a float located in the dialysate inflow line, indicating flow, the float will drop to the bottom of the indicator. There usually is a manually operated control to initiate the bypass mode. Failure of the bypass valve during dialysis is a critical and dangerous situation.

Rinse Mode

The rinse mode on dialysis machines overrides the bypass system. It allows rinsing and disinfection of the entire fluid pathway. It should never be activated while a patient is on dialysis. In new-model machines, the blood pump cannot be activated when the machine is in rinse mode.



• **Fig. 9.7** Bypass Valve Activated. (From Pittard J. *Hemodialysis Nursing, Training Manual*. 7th ed, version 7.0. Santa Monica, CA; 2003, with permission.)

Dialysate Pressure Monitor

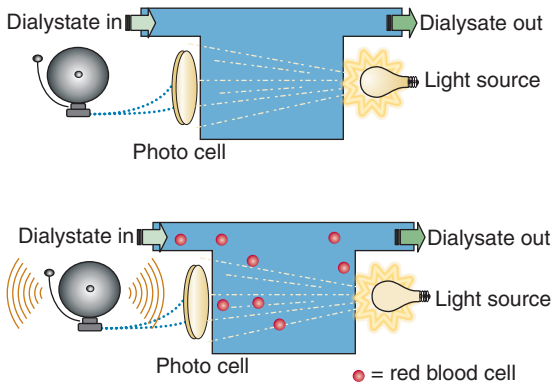
The dialysate pressure monitor monitors ultrafiltration pressures. It is a critical function of dialysis therapy that ensures accurate and safe fluid removal from the patient. One method to regulate the patient's ultrafiltration is by application of transmembrane pressure (TMP). Newer machine models have ultrafiltration/volumetric control circuits. The dialysis personnel set the goal for the desired fluid removal, set the duration of dialysis, and activate the ultrafiltration control mode. The machine will automatically calculate and apply the required TMP to achieve the desired ultrafiltration.

Volumetric control systems have different design features. A common design uses balancing chambers to precisely measure fluid volume entering and leaving the dialyzer. These machines automatically adjust the TMP. Volumetric control systems use matched pumps, usually diaphragm pumps. The pumps are controlled by valves and are integrated after proportioning of dialysate. Valves located above and below the balancing chambers open and close to direct the flow of fresh and used dialysate. Fresh dialysate is pushed out to dialyze, whereas used dialysate is pushed out to drain. The two chambers alternate functions, creating a constant flow of fresh dialysate. The system is a closed loop with both chambers exactly balanced. Air is removed from the used dialysate in a separation chamber to ensure accurate measurement.

It is recommended that a pressure-holding test be performed predialysis to ensure proper functioning of matched pumps and appropriate sealing of the valve. This tests the integrity of the diaphragms to ensure that they are free from defects or flaws. Bad valve seals can cause inaccurate ultrafiltration that is potentially catastrophic with high-flux dialyzers. These tests can be performed manually or automatically, depending on the machine model.

Blood-Leak Detector

This monitor functions by transmitting filtered or unfiltered light through a column of effluent dialysate that has exited the dialyzer (Fig. 9.8). Tears or leaks in the dialyzer



• **Fig. 9.8** Blood-Leak Detector. (From Pittard J. *Hemodialysis Nursing, Training Manual*. 7th ed, version 7.0. Santa Monica, CA; 2003, with permission.)

membrane cause RBCs to leak into the dialysate, interrupting the light transmission. The machine response to a blood leak alarm is an audible alarm, a visual alarm, the blood pump stops, and the venous line clamp engages.

It is recommended to have a blood-leak detection threshold set at 0.25–0.35 mL of whole blood per liter of dialysate. False blood-leak alarms can be caused by the presence of air bubbles in the path or by cloudy or dirty optical lenses.

Blood-Leak Detector Monitoring

If the machinery indicates this alarm, a stat Hemastix (benzidine test strip) must be taken at the dialysate drain line. A positive Hemastix test indicates a blood leak. If the Hemastix is weakly positive and the patient is on a hollow-fiber dialyzer, it is possible to closely monitor the patient, observe the dialysate outflow for increased turbidity (indicates air bubbles or RBCs), and wait a few minutes. The leaking fibers may seal or clot off. During this time, remove the ultrafiltration, decrease the blood flow rate, and attend the patient on a one-to-one ratio. If the patient cannot be continuously monitored, the dialyzer should be replaced.

If the repeat Hemastix is negative, dialysis can be continued. If the blood-leak alarm continues or if blood is visible in the dialysate lines, the dialysis should be stopped, and the dialyzer changed per unit protocol. The dialyzer should be discarded.

After a blood leak, it is important to clean the optical path of the blood leak detector. Always maintain a narrow range of sensitivity. Do not dialyze a patient with a faulty blood-leak detector. A major blood leak can be fatal.

Dialysate Flow

The dialysate flow rates may be preset or adjustable. The usual dialysate flow rate for conventional dialyzers is a minimum of 500 mL/min. For high-efficiency and high-flux dialyzers, it is usually 700–800 mL/min. It is counterproductive and provides an inefficient dialysis to use high blood flow rates with high efficiency or high-flux dialyzer with a dialysate flow of less than one and one-half the blood flow rate. Adequate dialysate flow is essential for efficient dialysis.

Dialysate Flow Monitoring

These alarm conditions include low incoming water pressure to the machine, dialysate pump failure, obstruction in the flow path, and power failure.

Most machines have a continuous audible alarm with these conditions. There are usually no alarms that alert the staff when the dialysate flow rate is set too low, for example, at 500 mL/min instead of 800 mL/min. Dialysis personnel must be diligent in monitoring this aspect of care.

Effluent Dialysate Line

Dialysis personnel must monitor the dialysate effluent line to the drain to ensure that it is not obstructed and is properly placed in the drain. An obstruction can cause backpressure into the dialysate compartment and may decrease the dialysate flow rate.

Electrical Safety

Dialysis machines pose a risk of electrical shock to a patient or staff member. All electronic equipment must be inspected and tested on a periodic basis. The staff members, most frequently in the patient care areas, must accept responsibility for identifying and reporting any potential hazardous conditions. All electric components should be adequately isolated from liquid leaks and the outside of equipment shielded from liquid spills. Electric components must be plugged into the correct socket, and grounded plugs used. Electrical safety classes and safe use of equipment are mandatory for all dialysis personnel.

Other Areas to Monitor in the Dialysate Circuit

Additional areas requiring monitoring include correct prescription, absence of impurities (cleaning and disinfecting agents), microbiologic count, and absence of potential pyrogenic agents.

Dialysate Prescription

Dialysis personnel must confirm that the physician's orders prescribing the dialysate content match the delivered prescription of dialysate. The dialysate prescription is not static. Some physicians model and individually tailor sodium, potassium, calcium, magnesium, and dextrose. A major problem with using many individualized dialysate formulas in one facility is the increase in risk for error by personnel. The more variables that exist in a dialysis unit, the greater the inherent risk of staff errors increases as the variables increase in a dialysis unit.

Dialysate Prescription Monitoring

Staff must check and verify all dialysate concentrate containers for the appropriate content. Each container must be clearly labeled. No unlabeled dialysate concentrate container should be used. Labels must include each electrolyte; the amount, time, and date mixed; and the name of the person performing the task. All additives must be properly recorded on the labels. This is especially important for the bicarbonate concentrate, which must be used within a 24-hour period after mixing. The 24-hour precaution reduces the risk of bacterial growth and calcium and magnesium precipitation. The correct dialysate concentrate must be attached to the correct concentrate port on the dialysis machine.

Sterility and Impurities

The dialysate solution is very clean but not sterile. Most dialysis facilities in the United States use reverse osmosis (RO) systems to filter the feed water. Theoretically, the product water should be sterile. But, as the water courses through the plastic piping of the dialysis unit to the dialysis machine and traverses through the fluid pathway, it comes in contact with bacteria, endotoxins, pyrogens, and other impurities.

All fluid pathways in the dialysis machines must be routinely rinsed, cleaned, and disinfected. The rinsing and cleaning process keeps the internal environment of the dialysis machine clean and free of cellular debris or deposits for proper operation. The disinfection eliminates bacterial growth and prevents the risk of pyrogen reactions. Each dialysis facility uses different techniques to achieve this end.

Inadequate cleaning and disinfection of the water treatment system, dialysate delivery system, and dialysate concentrate containers lead to high bacterial counts. Inadequate disinfection can be due to lack of frequent disinfection, too low concentrations of cold chemical disinfectants, and inadequate contact time of the disinfectant.

AAMI requires a minimum of once-a-month testing. The testing is to validate the proper disinfection of equipment. The sample for testing the fluid delivery system is taken "at the termination of dialysis at the point where dialysate exits the dialyzer." Industry standards recommend additional sampling. Samples from dialysate concentrate containers and mixing tanks should be taken after the longest period between disinfection of these containers and after the longest storage time for the concentrate.

All test results must be documented.

Microbiologic Testing

Microbiologic monitoring is to check for the presence of live bacteria. The number of living bacteria in a set volume is reported as the colony count or colony-forming units per milliliter (CFU/mL). Bacterial testing requires that the total viable microbial count is not to exceed 200 colony-forming units per milliliter (Table 9.2). Microbial test results must be documented. Microbial counts exceeding the industry standards require analysis and a more frequent and vigorous disinfecting routine. It is recommended to take action if levels exceed 50 CFU/mL. "Action" is to disinfect the system and repeat cultures at several sites. The action may be to repeat the culture, particularly if only one in a set of cultures was above the action limit.

TABLE 9.2 AAMI Microbiologic Standards

Fluid	Bacteria Maximum Action Level	Endotoxin Maximum Action Level
Water to prepare dialysate, to reprocess dialyzers, and prepare germicides	<200 CFU/mL ≥50 CFU/mL	<2.0 EU/mL ≥1 EU/mL
Dialysate	<200 CFU/mL ≥50 CFU/mL	<2.0 EU/mL ≥1 EU/mL
Bicarbonate concentrate	<200 CFU/mL ≥50 CFU/mL	<2.0 EU/mL ≥1 EU/mL
Minimum frequency	Monthly	Monthly

AAMI, Association for the Advancement of Medical Instrumentation.
From Pittard J, De Palma J. *Dialysate Monograph*. 1st ed. Glendale, CA: Hemodialysis, Inc.; 2013.

Bacteria in Bicarbonate Concentrate

The acid dialysate concentrate is bacteriostatic, inhibiting growth or multiplication of bacteria. However, bicarbonate powder used to make bicarbonate concentrate can be contaminated with bacteria, molds, and/or pyrogens. Failure to properly clean and disinfect all areas where water and dialysate travel leads to bacterial growth, often with *Pseudomonas*, in the fluid pathways.

Test for Endotoxins

Endotoxins are bacterial lipopolysaccharides. They are substances released from cell walls when a microorganism is broken down or dies. Their origin is usually from gram-negative bacteria. The presence of endotoxins is measured using the limulus amebocyte lysate (LAL) assay. The LAL concentration should be less than two endotoxin units (EU) per milliliter (<2 EU/mL). It is recommended to take action if levels exceed 1.0 EU/mL.

Pyrogens

High bacterial counts predispose to pyrogen reactions. The most common type of pyrogen is from fragments of dead bacteria. However, any type of cellular debris, even if it is sterile, can cause pyrogen reactions. An increase in pyrogen reactions is associated with the use of high-flux dialyzers and bicarbonate dialysate.

The lack of adequate removal of bacteria and bacterial end products from the dialysate solutions and/or fluid pathway of the dialysis machines is invariably the principal cause of these pyrogenic reactions. Dialysis facilities that practice scrupulous water disinfection and control, even with reuse of dialyzers, have virtually no pyrogenic reactions.

Some literature invokes the increased porosity of the high-flux membrane to whole bacteria as a substantial cause of pyrogen reactions. However, even in dialysis units using reprocessed high-flux dialyzers, correcting the high microbial counts of the feed water and delivered dialysate invariably eliminates all pyrogen reactions.

Ultrapure Dialysis Fluid

The term "ultrapure" has been in use since the early 1990s. The microbiologic quality of dialysis fluid dictates the definition of ultrapure dialysis fluid. This fluid, composed of ultrapure dialysate and water, should contain a bacteria count less than 0.1 CFU/mL and endotoxin levels less than 0.03 EU/mL. These levels, established in the European community, have much stricter standards for microbiologic testing as compared to the standards in use in the United States.

The European Best Practice Guidelines for Hemodialysis recommend the use of ultrapure dialysis fluid as a goal for all patients and all modalities, along with recommendations on testing to validate the purity of the fluid. Evidence suggests that the use of "ultrapure" dialysate diminishes inflammatory processes seen in the dialysis patient population. Improving the overall morbidity and mortality rates.

Innovative approaches are currently in use in the United States. Bacterial and pyrogen filters for manufacturing ultrapure dialysis fluid are being integrated into the fluid delivery systems.

Cleaning and Disinfection

It would seem obvious that cleaning and disinfection of the dialysis machinery should only be done after all patients have been completely disconnected. Although obvious, there are several reported instances of patients being "bleached" or "cooked" when the respective cleaning procedure began before all patients were disconnected.

Central System Hazard

A central fluid-delivery system that services more than one room carries the enormous risk of this lethal misadventure. A careful and thorough bed and chair check by two individuals must be performed to verify that no patient is on dialysis in that setting.

Routine Cleaning

Routine cleaning of fluid delivery systems is accomplished by rinsing with purified water (AAMI standard) and acid cleaning of the fluid pathway on a daily basis. Acid cleaning minimizes the buildup of calcium precipitate that is associated with bicarbonate dialysate. Acid cleaning does not disinfect the machine. Acid cleaning is accomplished with the use of acetic acid (5%) or vinegar, citric acid, peracetic-based disinfectants, and acid concentrate. A minimum of a 5-minute water rinse is recommended before acid cleaning.

A thorough rinse of the dialysis machine must be done before patient use or chemical disinfection. Acetic acid can easily be tested for residuals by using pH test paper.

Fluid Delivery System Disinfection

Disinfection of the fluid delivery system is done by heat and/or chemical disinfection. Chemical disinfection is done usually once each week or more often if necessary. Frequency of disinfection depends on routine bacterial counts and the orders of the medical director. Samples for bacterial counts should be taken before disinfection.

Heat Disinfection

Certain models of fluid delivery machines are equipped to use heat disinfection. In most cases, this is done on a daily basis. Heat disinfection occurs with water heated to about 85°C in the internal fluid pathway of the dialysis machine. The average length of heat exposure is about 30 minutes. It is important to follow the manufacturer's recommendations. If the machine is to be used following heat disinfection, it is critical to allow the proper cooling down cycle before patient use. Most machines using heat disinfection have a built-in safety feature that will not allow the machine to go into the "dialyze" mode until the temperature has dropped below 42°C.

Chemical Disinfection

Chemical disinfection may be done with a variety of chemicals. The most common chemical disinfectants in use are sodium hypochlorite, peracetic acid, and formaldehyde. A thorough water rinse is essential when using corrosive chemicals for disinfection. When using chemical disinfectants, it is important to remember that all disinfectants require a certain amount of contact time. High microbial counts in water require longer contact times.

Fluid pathways that have dead spaces, blind loops, or inactive dialysis stations that are improperly shunted to drain are especially hazardous. All dead spaces are difficult to disinfect.

All machines require labeling with a sign indicating the presence of the chemical disinfectant and the need for residual testing before the disinfection is deemed complete.

Sodium Hypochlorite

Sodium hypochlorite (bleach) is a cold disinfectant. It is available in different concentrations ranging from 5% to 10%. The advantages of sodium hypochlorite are its low cost, its effectiveness, and safety. Free chlorine is a strong oxidant. It effectively cleans and eliminates any cellular debris in the fluid pathway that may interfere with the machine operation.

Residual testing for sodium hypochlorite is simple and done with chlorine reagent test strips that test down to 0.5 parts per million (ppm). The residual test is very sensitive. Sodium hypochlorite in minute amounts greater than 1:25,000 produces hemolysis. Some dialysis units clean their bicarbonate concentrate plastic containers with bleach but do not carefully rinse or test for residual chlorine before refilling with bicarbonate concentrate. This allows bleach to be dialyzed into the patient, causing a low-level persistent hemolysis that is ignored or attributed to functional iron deficiency. Failure to perform residual testing will result in acute hemolysis or slow hemolysis that may go undetected.

Formaldehyde

Formaldehyde is a cold sterilant that effectively kills all microorganisms, including spores and resistant viruses, when used in proper concentrations and given adequate contact time. There are several reports of serious to deadly septicemia, with inadequate formaldehyde concentrations being used to disinfect the fluid path of dialysis machinery. It is the most common periodic disinfectant used for fluid-delivery systems. It is an inexpensive and stable solution with a long shelf life.

Formaldehyde is a gas that is dissolved in water to form the compound formalin. Formalin is the saturated solution

of formaldehyde in water. A 100% formalin solution is equivalent to 37%–40% formaldehyde. In dialysis, a 4% formaldehyde (11% formalin) concentration is used.

Concentrations lower than 4% formaldehyde do not kill *Mycobacterium chelonae* in water adequately. The formaldehyde gas is irritating to the eyes and has an offensive odor. Gloves must always be worn when handling formaldehyde to prevent dermatitis and allergic sensitivities. The room must be well ventilated. Any splashing must be minimized. A face shield gives total protection to the face. Minimally, eye protection (goggles) must be worn when handling formaldehyde.

Formaldehyde has no cleaning properties. Formaldehyde denatures protein and fixes most cellular debris. Therefore, before its use, the fluid pathway requires water rinsing and use of another chemical substance to remove any existing cellular debris and deposits. The fluid pathway of the fluid-delivery machines is filled with formaldehyde after cleaning to destroy any and all microorganisms. Generally, the formaldehyde is left in the machine overnight for effective contact time.

Sensitive residual testing is now available. Indicator test strips are now on the market to test for residual formaldehyde to a sensitivity of 1.0 ppm. The same principles apply to this cold sterilant as described for peracetic acid. In the past, safety tests for formaldehyde called for the use of Schiff reagent. Schiff reagent will test to 5 ppm. The newer indicator test strips are more sensitive.

There have been several outbreaks of feed water being contaminated with residual formaldehyde, which led to a number of dialysis patients on single patient machines becoming seriously ill with shock, coma, and semilethal consequences.

Peracetic Acid

The use of a stabilized mixture of peracetic acid, hydrogen peroxide, and acetic acid is probably the cold sterilant of choice for fluid delivery systems. Unlike formaldehyde, this mixture leaves no toxic residues. It decomposes into oxygen and acetic acid after reacting with organic material. The odor is pungent, similar to the smell of vinegar.

The mixture of peracetic acid, hydrogen peroxide, and acetic acid acts as a cleaning agent in addition to a cold sterilant. The mixture is a strong oxidant that readily cleans all cellular debris and precipitates or scales in the machines when used routinely. As a cold sterilant, it is effective with an 11-hour contact time. Because it is a strong oxidant, the manufacturer's recommendations must be followed carefully so that materials in the machines will not be adversely affected.

Test strips are available to check for the presence or absence of the peracetic acid mixture. Indicator test strips ensure the presence of this cold sterilant in the machines. After the peracetic acid mixture is rinsed from the machine, residual test strips test for the absence of the peracetic acid mixture. The residual testing is very sensitive, testing down to <1 ppm.

Because the peracetic acid mixture is a strong oxidant, its handling requires careful attention to avoid chemical burns. Gloves and face protection are mandatory. Accidental contact exposure to this chemical requires water flushes and medical attention similar to those described for formaldehyde.

Regardless of the type of cleaning or disinfecting agent used in the facility, a thorough water rinse must be done before adding chemicals and after cleaning and disinfection. Safety tests must be done after the final rinse to validate the absence of the chemical used. It is dangerous to rely on a timed rinse without the use of a valid safety test. Residual testing prevents patient injury due to chemical exposure.

General Principles for Chemical Disinfection

Time is an important factor in chemical disinfection. Total disinfection requires adequate time exposure of the chemical to the organisms to be killed. The concentration of the chemical, temperature, and the number of organisms to be killed determine the amount of exposure time. The greater the number of organisms to be killed, the longer is the exposure time needed. Organisms such as spores require longer exposure time than bacteria.

Chemical disinfectants need to remain moist for effectiveness. A chemical disinfectant that dries up is no longer effective. The concentration of the chemical must be in accordance with the manufacturer's recommendations. Lower concentrations may not be effective in killing all microorganisms, whereas concentrations that are higher may not be more effective. Blood and organic matter decrease the effectiveness of the chemical disinfectant. Chemical disinfectants should not be mixed, as mixing can alter their activity.

Dialysate systems must not have any dead spaces. A poorly designed dialysate system with dead spaces is impossible to disinfect adequately. To assess adequate chemical disinfection, monitor the equipment with cultures.

Additional principles include the following: (1) do not use chemical disinfectants beyond their expiration date, (2) always label equipment that contains a chemical disinfectant, and (3) perform an adequate water rinse prior to and after all chemical disinfection and perform the appropriate safety test after all chemical disinfection to ensure the absence of the chemical (do not rely on a timed rinse).

Documentation of Dialysate Monitoring

Document the performance and results of all safety tests on the patient Daily Dialysis Record and/or the machine or log sheet. Documentation or charting of all activities in dialysate monitoring is critical for patient safety. Do not initiate dialysis until all of the appropriate checks are complete and recorded according to the established policies in the facility.

Education of all staff members is critical to a safe and well-run dialysis unit. In-service education must be given for any new dialysate concentrates, preparation of dialysate concentrates, safety tests, and fluid delivery systems. There

TABLE 9.3 Risks to Patients With Inadequate Monitoring

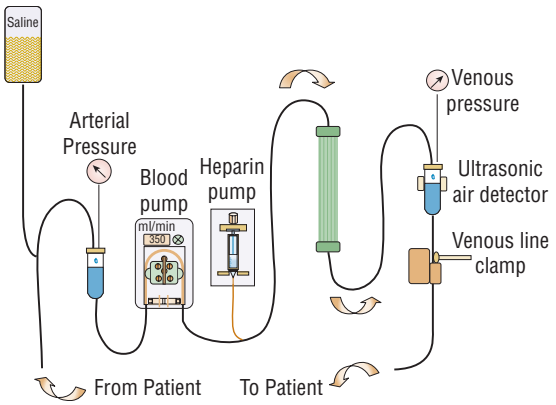
Problem	Potential Risk to Patient
Wrong prescription	Electrolyte imbalances, especially with potassium, leading to cardiac arrhythmias and cardiac arrest
Conductivity low	Hemolysis—death
Conductivity high	Hyperosmolar coma—death
High temperature	Hemodialysis—death
Dialysate flow rate absent	No dialysis with risk of serious electrolyte imbalances, especially hyperkalemia, cardiac arrhythmias, and cardiac arrest
Dialysate flow rate low	Inadequate and inefficient dialysis
Residual chemicals (bleach, formaldehyde, peracetic acid)	Hemodialysis—death
High bacterial count	Mild to severe pyrogen reaction

From Pittard J, De Palma J. *Dialysate Monograph*. 1st ed. Glendale, CA: Hemodialysis, Inc.; 2013.

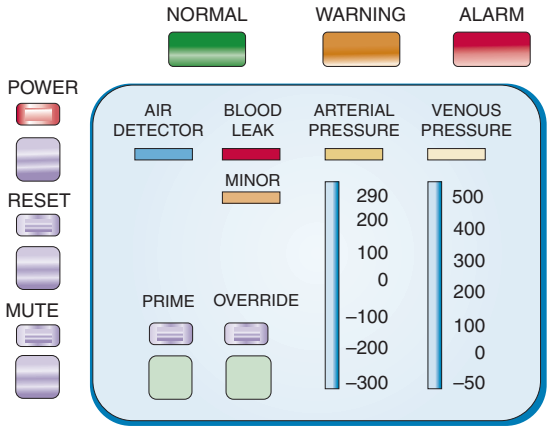
are many risks (Table 9.3) to the patient's well-being with inadequate monitoring of the dialysate compartment prior to or during the dialysis treatment.

The Blood Circuit

The blood (extracorporeal) circuit (Fig. 9.9) monitors pressures in the arterial and venous blood lines, and the integrity of the circuit for the presence of air and blood leaks. The



• **Fig. 9.9** Blood (Extracorporeal) Circuit. (From Pittard J. *Hemodialysis Nursing, Training Manual*. 7th ed, version 7.0. Santa Monica, CA; 2003, with permission.)



• **Fig. 9.10** Blood Circuit Monitors. (From Pittard J. *Hemodialysis Nursing, Training Manual*. 7th ed, version 7.0. Santa Monica, CA; 2003, with permission.)

four main blood circuit monitors (Fig. 9.10) are the arterial pressure monitor, venous pressure monitor, air-foam detector, and blood-leak detector.

The blood-leak detector acts as a blood-circuit alarm but is entirely incorporated within the dialysate circuit and has already been described. The machinery responds to blood-circuit alarms by activating an audible alarm, a visual alarm, stopping the blood pump, and engaging the venous line clamp to stop the blood flow through the blood circuit.

Additional areas to monitor in the blood circuit are blood flow rate, heparin therapy, and normal saline supply.

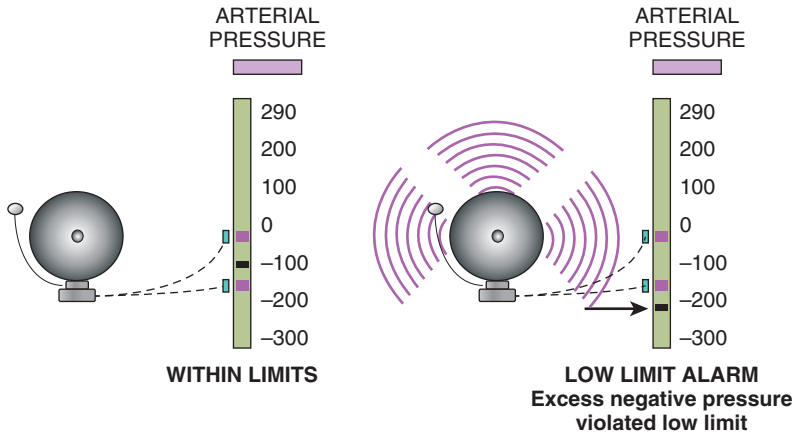
Arterial Pressure Monitor—Pre–Blood Pump

The arterial pressure monitor measures the pressure in the arterial blood line between the patient's arterial access and the blood. With the blood pump set to blood flow rates greater than 200 mL/min to as high as 450 mL/min, the pressure in this blood tubing segment is commonly subatmospheric to negative. This portion of the blood circuit can be a source of air entry into the blood circuit and is considered a high-risk area.

The arterial pressure monitor is leak-free with adjustable high/low limits (Fig. 9.11), which reads negative and positive pressures in millimeters of mercury (mm Hg; 10% accuracy). This monitor requires a filter to prevent viruses, bacteria, or blood from being refluxed back into the arterial pressure monitor. This filter is essential, as viral hepatitis has been transmitted by contamination of air devices.

These filters or fluid barriers are called isolators and/or transducer filters/protectors. They protect the monitor from blood contamination and the spread of infection between patients. The pressure monitor lines must be unclamped and patent during dialysis. Some blood lines have collapsible pillow-shaped segments, which can initiate a false alarm.

During set-up, priming, and rinsing of the dialyzer, the high/low limits are opened. As soon as the dialysis treatment is initiated, the dialysis personnel must set the low, or negative, pressure limit just below the reading at the desired



• **Fig. 9.11** Arterial Pressure. (From Pittard J. *Hemodialysis Nursing, Training Manual*. 7th ed, version 7.0. Santa Monica, CA; 2003, with permission.)

blood flow. Upper and lower monitor limits should be set within 50–100 mm Hg of actual reading to detect problems. Newer machine models will automatically adjust the high/low limits approximately 50 mm Hg above and below the actual pressure.

Setting the low arterial limit close to the actual pressure, about 50 mm Hg below that pressure, will detect early drops in blood pressure with arteriovenous (AV) fistulas. Some units limit the minimum arterial limit to –100 mm Hg.

The greater the vacuum, the greater the risk of air entering this tubing segment from any crack, improperly glued or fitted joint, sample port, saline infusion line, or the patient's access. It is advisable to set the high limit just below zero, which will pick up a disruption of the arterial blood line from the fistula needle.

Arterial Pressure Monitoring

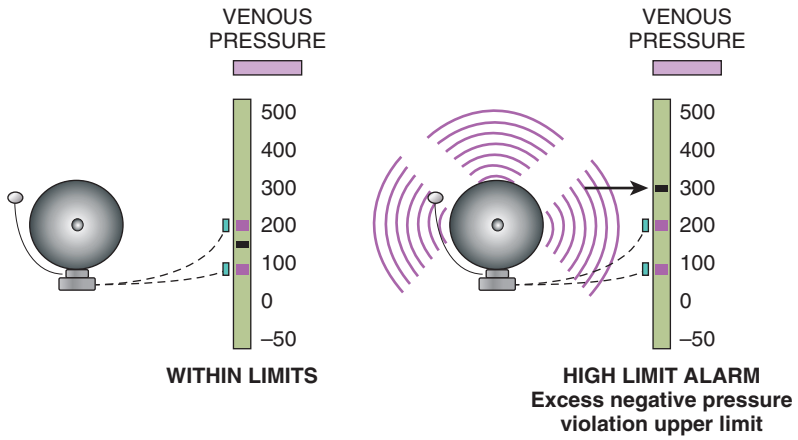
The usual causes of a low-limit arterial pressure alarm are a drop in blood pressure (only with AV fistulas), a kink in the arterial blood line between the access and blood pump, malpositioned arterial needle, or problem with arterial access, and a clotted arterial line. The circuit should always be checked for air bubbles.

The usual causes of a high-limit arterial pressure alarm are bloodline separation (only if the upper limit is set below 0 mm Hg), the saline infusion line is unclamped, an increase in patient's blood pressure, a leak in the circuit between the patient and the monitor, and torn blood tubing in the pump segment. It is important to check for leaking blood.

The appropriate response to pressure alarms is to, first, mute the audible alarm; second, investigate the problem; third, correct the problem; and fourth, restart the blood pump by pressing the reset/restart button. Do not restart the blood pump until the problem is corrected for patient safety. Failure to correct the problem will cause the alarm to reoccur.

Venous Pressure Monitor

The venous pressure monitor, located postdialyzer, monitors pressure at the venous drip chamber, the segment between the drip chamber and the patient's venous access, and the added intra-access pressure. The resistance to the blood flow entering the venous access causes the pressure to be positive (Fig. 9.12), above 0 mm Hg.



• **Fig. 9.12** Venous Pressure. (From Pittard J. *Hemodialysis Nursing, Training Manual*. 7th ed, version 7.0. Santa Monica, CA; 2003, with permission.)

The venous pressure monitor's structure and standards are similar to those described for the arterial pre–blood pump monitor. This pressure monitor requires protection by a filter or transducer fluid barrier.

Venous Pressure Monitoring

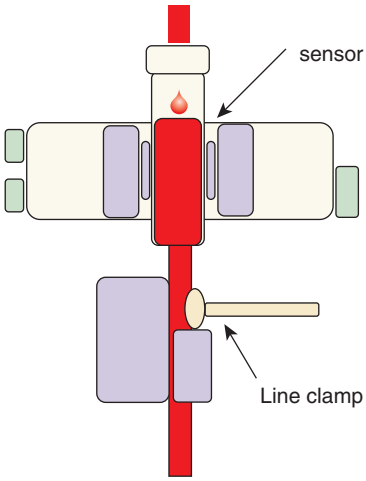
Causes of a high venous pressure alarm are a kink in the venous blood line between the drip chamber and patient's venous access, a clot in the venous drip chamber and/or downstream to the patient, and a malpositioned venous needle or problem with the venous access device.

Causes of a low venous pressure alarm are blood line separation or disruption of connections between the blood pump to and including the venous access; a kink in the blood line postdialyzer and pre–venous drip chamber; a clotted dialyzer; and a lowering of the blood-pump speed. Note that setting the low limit close to the operating pressure of the venous drip chamber can alert to a disruption of the blood circuit between the blood pump and venous access site. With a disruption of the circuit, the venous pressure will drop to 0 mm Hg.

It should be remembered that the venous pressure monitor reflects P_{BO} in the equation $TMP = P_{BO} - P_{DO}$. High venous pressures can result in too high ultrafiltration rates unless an ultrafiltration-controlled machine is being used.

Air-Foam Detector

The air-foam detector monitors blood in the venous tubing (Fig. 9.13) for the presence of air, foam, and microbubbles. It must be reemphasized that with almost all internal AV fistulas/grafts and venovenous dialysis, a significant subatmospheric pressure exists between the arterial access and the roller pump. There are many junctions and heat-sealed joints in this portion of the circuit. If the heparin infusion line is in the negative-pressure segment rather than post–blood pump, it may increase the risk for air entry. After the blood pump, the blood circuit is at considerable positive pressure, and air can enter only by pumping or injecting it into the remainder of the circuit. Air embolism is a preventable and very serious dialysis misadventure.



• **Fig. 9.13** Air-Foam Detector. (From Pittard J. *Hemodialysis Nursing, Training Manual*. 7th ed, version 7.0. Santa Monica, CA; 2003, with permission.)

Two types of air-foam detectors are in use: the ultrasonic and reflected light detectors. It is believed that only the ultrasonic device is currently being sold. Nevertheless, many of the reflected light-type devices are still in use. Surprisingly, there are no standards for permissible detection of air because either type of detector readily identifies gross air displacement of blood in the venous drip chamber when properly armed and functioning. Microbubbles from 5 to 500 µm in diameter represent a different problem as they stream along with the blood flow. These microbubbles are entrained in the bloodstream.

Although both types of monitors can detect microbubbles, their guaranteed detection requires a sensitivity setting that may result in many false alarms because of turbulence in fluid flow. The compromise is a sensitivity adjustment of the ultrasonic devices such that some false alarms occur that require the attention of dialysis personnel. In certain situations, microbubbles can go undetected and cause clinical air embolism. The current standards for these devices require response to air in blood, a blood and saline mixture, or saline. Only the ultrasonic device can meet this requirement. A dangerous aspect of the reflected light device is that it is effective only when sensing the whole blood of the patient. It cannot be accurately armed during priming, initiation, or rinsing.

Venous Line Clamp

An air detector alarm must activate the venous line clamp (Fig. 9.13). The venous line clamp must completely occlude the venous blood line and withstand an intraluminal pressure of 800 mm Hg. The venous line clamp should be constructed to not damage the blood lines and should not restrict the blood tubing when in an open position. The venous line clamp circuitry must interface with and stop the blood pump. Most integrated air-foam detectors meet all of these standards.

There are dialysis machines that are unsafe as they include the ability to dialyze with both the air-leak detector and venous line clamp disarmed and only some marginal indication of this disarmed state.

Air-Foam Detector and Venous Line Clamp Monitoring

With an air-foam detector alarm state, identify that the venous line clamp is engaged and the blood pump is stopped. Visually inspect the entire blood circuit from the venous access backward to the arterial end for the presence of air, foam, or microbubbles. Check the level in the venous drip chamber—it should be three-quarters full. Check that the venous drip chamber is properly placed in its holder, the level detector door is closed and latched, and the mesh in the drip chamber is below the air detector. Also, check if the air sensors are clean. Always validate the absence of air before restarting the blood pump and disengaging the venous line clamp. If air is present, disconnect the patient from the extracorporeal circuit.

Before beginning dialysis, make sure that the air-foam detector is turned on and operational and that the venous blood line is properly placed in the line-clamp holder. Ultrasonic devices are usually activated during priming of the circuit. Reflected light devices cannot be activated until whole blood at full hematocrit is in the venous tubing.

Because each brand of detector varies in its operation, ensure that dialysis personnel are aware of the type of device used in the facility and are in-serviced on its unique features and operation. Unfortunately, when staff pushes the RESET/RESTART button in responding to this alarm condition, the blood pump restarts. This can be a potentially deadly response. Microbubbles that may not be visible to the naked eye can flow into the patient. I advise staff to manually turn off the blood pump when responding to an air-in-blood alarm. After all inspections are complete, pushing the reset button will not automatically start the blood pump. However, if the problem is not corrected, the alarm will reoccur with no harm to the patient.

Four alarm conditions are outlined here for general information.

Alarm condition 1. Careful inspection reveals that the blood-air level in the venous drip chamber is normal and that there are no microbubbles (foam) in any portion of the line or dialyzer. This is a false alarm—release the line clamp and reset the detector.

Alarm condition 2. The blood level in the venous drip chamber has fallen. In response, check for upstream bubbles. If none is present, return the blood-air level to normal in the drip chamber with the usual technique, release the line clamp, and reset the alarm.

Alarm condition 3. There are microbubbles (foam) in the venous line. In response, clamp the venous line and the venous access line, directing attention to the patient in the event that emergency management of air embolism is necessary. Another person should remove the line from the air detector clamp, disconnect the patient from the blood circuit, and aseptically join the arterial and venous ends of the blood circuit for recirculation. Remove ultrafiltration, open the saline to remove air from the blood circuit, and collect it in the venous drip chamber. If this measure is successful, place the venous line into the air-detector line clamp and rearm the air-foam detector. If no further alarm is activated, reconnect the blood circuit lines to the patient and reinitiate dialysis.

Alarm condition 4. Gross air and bubbles fill the entire blood circuit, including the dialyzer. In response, clamp the "venous" line and direct attention to the patient for emergency management of air embolism. Dispose of the entire blood circuit, including the dialyzer, and set up a new one to reinitiate dialysis.

Heparin Infusion Pump

The heparin infusion pump is usually located in the post–blood pump segment. A heparin infusion line attaches to a syringe filled with heparin. This allows for the infusion of heparin during dialysis. An electric motor drives a piston to move the heparin plunger forward to infuse the heparin. Dialysis personnel must turn the heparin pump on and set the correct hourly infusion rate. No alarms occur if the pump is not turned on or an incorrect hourly infusion rate is set. Most machines have an audible alarm when the heparin level in the syringe is very low.

Heparin Infusion Pump Monitoring

Personnel must make sure they are using the correct-size syringe based on the way the heparin pump is calibrated. Make sure the syringe and plunger are placed properly in the holder. Check that the pump is on and the variable hourly rate is set correctly. Implement hourly checks to ensure the correct infusion of heparin therapy. Newer machine models allow the personnel to program the heparin bolus, infusion rate, and length of time for the infusion.

Blood Flow Rate

The blood flow rate is an important parameter that influences the efficiency of dialyzer clearance. All blood pumps have an on/off switch and an adjustable variable speed pump. There are no machine alarms if the desired blood flow rate is not set correctly.

Blood Flow Rate Monitoring

Double-check that the blood flow rate is properly set. A qualified person must calibrate blood pumps to ensure that the actual blood flow is comparable to the blood-flow setting. The facility must use appropriate blood-tubing size for proper occlusion of the roller pump. Inadequate occlusion causes backflow, foaming, and possibly hemolysis. Over occulsion causes tubing damage, blood leaks, and the potential for hemolysis.

Blood Pump and Blood Lines

Narrowed Blood-Pump Tubing Segment

In 1998, 30 patients in three different states in the United States developed hemolysis with or without chest pains, shortness of breath, nausea, or abdominal pain while undergoing hemodialysis. Two patients died. All of these catastrophes were due to a manufacturing defect in a small portion of the blood-pump segment of the blood tubing. The staff did not notice the defect when inserting the blood-pump segment. A marked narrowing of this segment induced massive hemolysis in these patients, which initially was unexplained and required a formal investigation by the Centers for Disease Control and Prevention (CDC).

Kinked Arterial Blood Lines

In a 1-year period, from December 1989 to December 1990, a total of 10 hemolytic reactions occurred in an outpatient hemodialysis unit. Eight patients were hospitalized, and one died. All patients developed severe abdominal or back pain an average of 2.5 hours into a 4-hour hemodialysis session using bleach-formaldehyde reprocessed

hollow-fiber Cuprophan dialyzers. All had visible hemolysis in a spun hematocrit, seven had a significant decrease in hematocrit, and six developed pancreatitis. Hemolytic reactions continued despite changing to 15-gauge needles, removing bleach from the reuse procedure, and stopping reuse of the dialyzers.

Investigation of each episode failed to find an abnormality in dialysate temperature or tonicity; dialysate or water levels of copper, zinc, nitrates, chloramine, or formaldehyde; or blood pump or venous alarm. On the eighth hemolytic episode, a dialysis staff member noted a kink in the arterial blood line. Two subsequent hemolytic reactions occurred; in each, kinks were found in the arterial blood line, either in the excess tubing between the blood pump and drip chamber or in the predialyzer segment. No further hemolytic reactions occurred after changing to a new arterial blood line without redundant tubing and securing all lines.

IV Saline Infusion

Access to normal saline (0.9% NaCl) into the extracorporeal circuit occurs via the saline administration line located at the beginning of the arterial blood circuit. Normal saline is used to prime the dialyzer and blood tubing for patient use, to replace volume in the patient during dialysis, and rinse the RBCs at the conclusion of dialysis.

IV Saline Infusion Monitoring

Personnel must make sure an adequate amount of normal saline is available for immediate use during the dialysis treatment. Normal saline drips should be discouraged. Although normal saline comes in collapsible plastic bags, if these accidentally empty during dialysis, a few hundred milliliters of air will enter the blood circuit, possibly causing an air embolism.

Conclusion

The world of dialysis has undergone many changes. The fluid delivery systems are much more sophisticated and dialyzers more efficient. No amount of electronic machinery, fail-safe devices, flashing lights, sirens, dials, or protocols can take the place of an alert and well-trained dialysis staff member. Non–registered nurses or patient care technicians (PCTs) perform 75% of direct patient care of ESRD patients in the United States, and it is essential they understand potential alarm situations and are thoroughly trained to ensure safe dialysis treatment.

Recommended Reading

Anonymous. Multi state outbreak of hemolysis in hemodialysis patients, Nebraska and Maryland, 1998. *MMWR Morb Mortal Wkly Rep.* 1998;47:483–484.

The author points out a series of misadventures heretofore never described. In three states, a total of 30 patients developed hemolysis while undergoing hemodialysis. Following an extensive investigation to rule out the cause of hemolysis, it was determined that the patients dialyzed using the same manufacturer's blood tubing. An abnormal narrowing of the aperture of the manufactured blood line, causing a mechanical lysis of the RBCs, was discovered. All blood lines were recalled. These resulted in hemolysis, serious illness, and death.

Association for the Advancement of Medical Instrumentation (AAMI). *Dialysate for Hemodialysis (RD52:2004).* Arlington, VA: AAMI; 2004.

Association for the Advancement of Medical Instrumentation (AAMI). *Water Treatment Equipment for Hemodialysis Applications and Related Therapies (RD62:2006).* Arlington, VA: AAMI; 2011.

The AAMI developed water quality standards for the water used in hemodialysis. The American National Standards Institute (ANSI) adopted the standards established by AAMI. Standards currently in use are ANSI/AAMI RD52:2004 and, most recently, RD62:2006. These standards are included in the CfCs. The standards address both the facilities (users) and the manufacturers. Incorporated into these standards are recommendations of the Food and Drug Administration (FDA). The FDA bases its recommendations on a study on risks and hazards of hemodialysis devices. The AAMI standards for facilities address two basic categories, microbiologic and chemical contaminant monitoring.

De Palma JR. Bicarbonate Dialysis & Water Treatment. *Contemporary Dialysis & Nephrology.* 1988;9:20–21. 41.

The author, Dr. De Palma, cites that in the beginning of hemodialysis, acetate was the buffer used. It took years before bicarbonate replaced acetate as a buffer. This article reviews both buffer bases and their strengths and weaknesses. Acetate as a buffer was initially used because it was bactericostatic, easy to mix, and stable in solution. However, cases of patients developing pulmonary problems, headaches, nausea, vomiting, and hypotension were cured when bicarbonate as a buffer was used in Dr. De Palma's dialysis clinics. The company Cobe, Inc., was contacted and then produced their own bicarbonate concentrate, based on Dr. De Palma's work. Several other companies produced bicarbonate, including liquid bicarbonate, which proved to grow bacteria.

De Palma JR. Bleach & Murphy's Law. *Contemporary Dialysis & Nephrology.* 1988;9:30–31. 39.

The author, Dr. De Palma, a nephrologist, and early pioneer in hemodialysis, warns all hemodialysis staff to expect the unexpected, that if anything can go wrong, it will and compromise patient safety. Since the 1960s, Dr. De Palma has been building and running many dialysis clinics. Along the way, he encountered many misadventures that were unknown to the dialysis community. I concur with his explanation of "Murphy's Law" and that no machinery can substitute for competent human care.

European Best Practice Guidelines for Haemodialysis (Part 1). SECTION IV. Dialysis fluid purity. *Nephrol Dial Transplant.* 2002;17(suppl 7):46–62.

This article discusses various aspects of using ultrapure water. "Ultrapure" is defined as water virtually free from bacteria and endotoxins with microbiologic counts containing < 0.1 mL of colony-forming units/mL (CFU/mL) and endotoxin units of < 0.03 endotoxin units/mL (EU/mL). This is the standard in Europe but not in the United States or around most of the world. The benefits to the dialysis population in improving the overall morbidity and mortality rates are discussed. It should be mentioned that absolutely pure water is corrosive and will leach metals such as iron and copper from piping, caveat lector.

Gutch CF, Stoner MH, Corea AL. *Hemodialysis for Nurses and Dialysis Personnel.* 6th ed. St. Louis: Mosby; 1999:54–56. 59-65. ISBN: 0-8151-2099-0.

The authors presented the material in a different format from most books. Questions are presented, followed by descriptive answers that are intended to give the reader a basic understanding of the information. It is one of the best educational books for nurses and patient care technicians in the field of dialysis.

Yukihiro Nosé. Manual on Artificial Organs. Vol. I. In: *The Artificial Kidney.* Saint Louis, MO: CV Mosby Company; 1969:120–151.

Dr. Nosé's chapter on "Dialysate Supply Systems" published in 1969 presents the information on the chemistry of dialysate, dialysate composition, water for dialysate, final checks for dialysate composition, and all aspects of the equipment used in that era. It is clearly written and the concepts presented are easy to understand. The diagrams are clearly presented. The fundamental information remains a classic and applicable today.

Pittard JD. *Hemodialysis Nursing—Version 7.0.* Glendale, CA: Hemodialysis, Inc; 2003.

The author of this syllabus distills into an outline and into one resource the knowledge and experience acquired in two and one-half decades of teaching. This syllabus is primarily a teaching tool for both nurses and hemodialysis technicians, to assist them during the classroom lectures. It contains core lecture information taught in Ms. Pittard's hemodialysis training program. The classroom lectures are augmented with slides of bulleted text and colored graphics. This syllabus is derived from these slides and contains the course outline, lecture objectives, elemental lecture content, and recommended readings. I referred to the lectures that directly pertain to dialysate, the fluid delivery system, and monitors in dialysis.

Pittard JD, De Palma JR. *Monitors.* Glendale, CA: Hemodialysis, Inc; 2004:20–76.

The authors wrote this monograph as a home study course for dialysis nurses and technicians, who are awarded 30 contact hours of continuing education on completion of the monograph posttest. This monograph describes the machinery and personnel monitoring of the hemodialysis process. It is an in-depth review of hemodialysis safety monitors, covering both blood and dialysate circuits. Most, if not all, information is obtained from clinical research and actual hemodialysis experience. Expert and seasoned MDs and RNs in the ESRD field have reviewed all.

Pittard JD, De Palma JR. *Principles of Dialysis.* 3rd ed. Glendale, CA: Hemodialysis, Inc; 2006:65–85.

The authors of this monograph, recently updated to the third edition, covers acute and chronic renal failure, principles of hemodialysis, application of diffusion and ultrafiltration, dialysate solution, dialyzers, the hemodialysis system, the hemodialysis prescription, dialysis dose, access to the circulation, anticoagulation therapy, and alternative therapies. This monograph is a home study course for dialysis nurses and technicians, who are awarded 30 contact hours of continuing education on completion of the monograph posttest.

Pittard J, De Palma J. *Dialysate Monograph.* 1st ed. Glendale, CA: Hemodialysis, Inc; 2013.

The authors of this monograph thoroughly discuss the composition and clinical use of hemodialysate. Knowledge of the fundamental principles regarding the preparation and clinical applications will help the reader provide better care to the ESRD patient. It covers all of the new and current regulations regarding dialysate, including mixing, distribution, labeling, and use. This monograph is a home study course for dialysis nurses and technicians, who are awarded 30 contact hours of continuing education on completion of the monograph posttest.

Sweet SJ, McCarthy S, Steingart R, Callahan T. Hemolytic reactions mechanically induced by kinked hemodialysis lines. *Am J Kidney Dis.* 1996;27:262–266.

The authors discuss 10 hemolytic events occurring in the course of 1 year. This article describes blood lines being kinked. Kinks originated in the arterial blood line due to excess tubing between the blood pump and drip chamber or in the predialyzer segment. The elimination of kinks in the tubing resolved the problem. This emphasizes the importance of absolute mandatory training required of staff that provides direct patient care and the attention to detail that must be adhered to, even though blood tubing placement is a routine procedure.

The Department of Health and Human Services Center for Medicaid and Medicare Services (CMS). Conditions for Coverage (CfCs): Subpart B—patient safety, 494.40. *Water and dialysate quality Fed Regist.* 2008;73(73).

The ESRD CfCs Final Rule modernizes Medicare's ESRD health and safety conditions for coverage and updates CMS standards for delivering safe, high-quality care to dialysis patients. The ESRD CfCs are the minimum health and safety rules that all Medicare and Medicaid participating dialysis facilities must meet in order to operate and be Medicare certified. This condition incorporates by reference the AAMI and American National Standard for Dialysate for Hemodialysis, 2004 (RD52:2004). This condition has "Tags" or "V" codes; V175-278 (> 100) addressing expected guidelines and specific conditions for facilities to meet. This Interpretive Guidance is to replace all previously released versions. Specific regulations regarding dialysate are included. First-time regulations specific for dialysate include mixing, distribution, labeling, and use. It is essential to incorporate these rules into training of staff.

Utoh J, Harasaki H. Damage to erythrocytes from long-term heat stress. *Clin Sci.* 1992;82:9–11.

The authors researched the effects of heat on erythrocytes, RBCs. In particular, they hypothesized that erythrocytes might be damaged at lower temperatures if incubated for prolonged periods. The study was conducted using healthy human donor blood. Various time frames and temperatures were used. The study showed that prolonged exposure induced hemolysis at 42°C. It is critical that dialysate temperatures be preset with the internal high limit set at no higher than 41°C (105.8°F). Dialysate temperatures in excess of 106°F induce RBC hemolysis. Careful monitoring is mandatory. Staff education is critical in this area. Under no circumstances should the high limit be adjusted above 41°C. It should be remembered that uremic RBCs are more osmotically fragile and have a shorter half-life than normal RBCs. It is reasonable to assume that these uremic RBCs are more sensitive to all mechanical and thermal causes of trauma than normal RBCs.

10

Methods of Hemodialysis Anticoagulation

DAVID I. ORTIZ-MELO, MD • EUGENE C. KOVALIK, MD, CM, FRCP(C), FACP, FASN

Introduction

During intermittent hemodialysis and continuous kidney replacement therapies (CRRTs), blood is continuously flowing between the patient's vascular access and the dialyzer. This extracorporeal circuit exposes blood to surfaces with variable degrees of thrombogenicity. Clotting of the circuit, specifically the microfibers of the dialyzer, is associated with decreased dialysis clearance. Furthermore, the inability to return blood from a clotted circuit to the patient results in approximately 150–200 mL of blood loss. In order to prevent thrombosis, malfunctioning of the circuit, poor solute clearance, and blood loss, some form of anticoagulation is usually warranted. At the same time, patients with end-stage kidney disease are also at increased risk of bleeding, mainly due to platelet dysfunction in part related to uremic toxins. Therefore, the ideal anticoagulant used during hemodialysis should efficiently prevent thrombosis during hemodialysis therapy but at the same time does not increase the risk of intradialytic and interdialytic bleeding. Moreover, the anticoagulation agent should be simple to administer, with minimal or no monitoring requirements, cost-effective, and well tolerated with no negligible adverse effects.

Different anticoagulation protocols have been described and are currently available, including (1) full systemic anticoagulation, (2) anticoagulation of the extracorporeal circuit with minimal systemic effects (regional anticoagulation), and (3) anticoagulation-free dialysis. Strategies to minimize the bleeding risks include the use of low-dose heparin or no-heparin hemodialysis protocols, use of heparin-grafted membranes, regular saline flushes, or predilution hemodiafiltration. Regional anticoagulation with citrate, prostacyclin, or heparin-protamine has been used with varying success. Other agents such as argatroban, recombinant hirudin, and heparinoids have also provided effective anticoagulation and represent a valid alternative in selected patients. In this chapter, we discuss these agents, the different protocols for intermittent hemodialysis anticoagulation, as well as important considerations under certain clinical scenarios. Anticoagulation for CRRT is discussed in more depth in Chapter 68.

Assessing Bleeding Risk

While the use of anticoagulation for intermittent hemodialysis is a relatively common practice, the decision whether to administer anticoagulation and which specific protocol to use should begin with a thorough clinical assessment of patient's bleeding risk(s).

Numerous individual clinical factors have been associated with an increased risk of bleeding in this patient population, including (Table 10.1):

- Thrombocytopenia (platelet count of $<20{,}000$ per microliter)
- Recent or active bleeding (<48 hours; gastrointestinal [GI], intra-abdominal, postsurgical, intracranial, or from dialysis access)
- Recent surgery (<72 hours)
- Concomitant use of systemic anticoagulants
- Bleeding diathesis or clotting disorders
- Pericarditis

Systemic Anticoagulation

Standard Heparin Anticoagulation

Unfractionated heparin (UFH) is the most commonly used anticoagulation agent during hemodialysis. UFH binds to the enzyme antithrombin III, inducing a conformational change that leads to an increased activity of this natural anticoagulant. This results in accelerated inactivation of coagulation factors, such as factor Xa and thrombin (Fig. 10.1). UFH is affordable, reliable, easily reversible, and requires minimal staff intervention after a patient's heparin dose is determined. UFH can also be safely used during pregnancy since it does not cross the placenta. Although heparin is relatively well tolerated, there are certain known risks and complications associated with its use, including increased risk of bleeding, heparin-induced thrombocytopenia (HIT), hypertriglyceridemia, hypersensitivity reactions, pruritus, osteoporosis, and rarely hyperkalemia.

TABLE 10.1 Categorization of Bleeding Risk

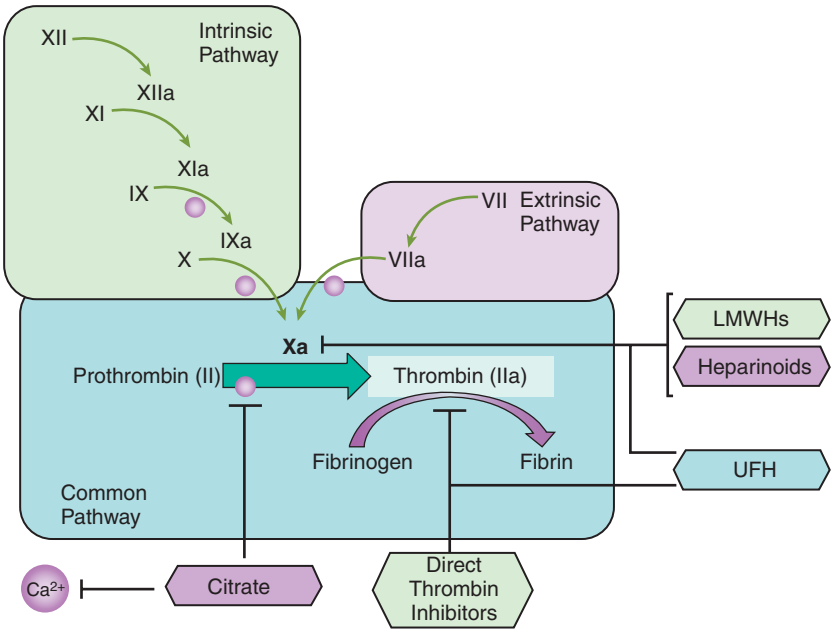
Medium Risk	High Risk
Pericarditis	Bleeding diathesis
Recent bleeding < 48 hours	Clotting factor disorder
Recent placement of tunneled catheter < 24 hours	Actively bleeding
Minor surgery < 72 hours	Eye or major surgery < 72 hours
Eye or major surgery within 3–7 days	Intracranial hemorrhage < 7 days

Modified from Saltissi D. Management of anticoagulation for hemodialysis. In: Nissenson AR, Fine RN, eds. *Dialysis Therapy*. Philadelphia: Hanley and Belfus; 2002.

UFH has a rapid onset of action and relatively short half-life (approximately 1 hour in dialysis patients). However, it is important to keep in mind, however, that there is interpatient variability in heparin metabolism during hemodialysis. Heparin activity is highly determined by patient weight and other variables, such as dialyzer absorption, erythropoietin dose, thrombogenicity of the extracorporeal circuit, blood flow, and length of the hemodialysis treatment among others.

Anticoagulation with UFH during hemodialysis can be monitored by the determination of activated partial thromboplastin time (aPTT), which is targeted to 1.5–2 times above baseline value. However, this method requires frequent testing leading to increased cost and repeated blood draws. Another option is the determination of activated clotting times (ACTs), which can be obtained with point-of-care devices. ACT is typically targeted to 80% higher than baseline value. However, ACTs are used infrequently because of the need to be rigorously standardized, resulting in quality assurance and regulatory issues. In general, most outpatient dialysis units do not routinely measure anticoagulation parameters unless there is clinical evidence suggesting of dialyzer clotting (i.e., visual clots, increased extracorporeal circuit pressures, etc.) or signs of over-anticoagulation, such as prolonged bleeding at needle puncture sites following decannulation. Except on rare occasions, we do not regularly monitor anticoagulation levels in the inpatient and outpatient facilities of our institutions.

Currently, there are no standardized heparin dosages for anticoagulation during hemodialysis in the United States. A number of empirically-based protocols exist to address the competing issues of clotting and postdialysis bleeding from venipuncture sites. These methods require minimal staff intervention and are standard in most outpatient hemodialysis



• **Fig. 10.1** Schematic Representation of the Coagulation Cascade and Targets of Different Anticoagulants. Unfractionated heparin *(UFH)* binds to antithrombin and indirectly inhibits both factor Xa and thrombin. Low-molecular-weight heparins *(LMWHs)* and heparinoids inhibit only factor Xa. Direct thrombin inhibitors, such as argatroban and recombinant hirudin, directly bind and block thrombin, the key enzyme that converts soluble fibrinogen into insoluble fibrin. Citrate chelates calcium (Ca^{2+}, circles), a key cofactor of many reactions in the coagulation cascade.

units; they are, however, unsuitable for patients with significant bleeding risks. Typically, the administration of heparin during hemodialysis requires an initial loading bolus, followed by a maintenance dose that can be given either as repeated separate boluses or as a continuous infusion. These strategies ensure systemic anticoagulation throughout the dialysis treatment. A routine repeated bolus regimen consists of an initial bolus of UFH (usually about 40–50 IU/kg body weight, or 2000–4000 IU) administered into the venous access needle, followed by a midtreatment dose of 1000–2000 IU to maintain suitable anticoagulation. Alternatively, heparin modeling can be performed using an initial bolus followed by a constant fixed infusion of heparin (usually 10–15 IU/kg body weight/h, or 500–2000 IU/h) to maintain an ACT of 200 to 250 seconds (normal ≈ 90 to 140 seconds). Heparin infusion should be terminated 30–60 minutes prior to the end of treatment to reduce postdialysis venipuncture bleeding. Some other protocols include the use of a single initial bolus dose with no maintenance doses, and the administration of a high bolus heparin dose (i.e., greater than 5000 IU) with decreasing infusion rates, as the treatment proceeds to minimize postdialysis bleeding. Furthermore, in facilities that practice dialyzer reuse, incorporation of a pharmacodynamic approach to heparin modeling has also been shown to increase dialyzer reuse rate.

The use of UFH with dialysis therapy ensures systemic anticoagulation throughout the dialysis treatment. It is reliable and requires minimal staff intervention after a patient's heparin dose has been determined. The three most commonly used standard anticoagulation regimens using UFH and different UFH protocols used in our institution are summarized in Tables 10.2 and 10.3, respectively.

Low-Dose Heparin

The use of minimum-dose heparin is an alternative anticoagulation strategy for patients with high bleeding risk who are unable to complete heparin-free hemodialysis due to frequent clotting. Currently, there are no standardized dosages for this protocol. Initially, the extracorporeal circuit is rinsed with 2000 to 5000 IU of UFH followed by a saline rinse to remove the unbound anticoagulant. Generally, patients receive boluses of 500 IU of heparin every 30 minutes to keep the ACT no higher than 40% above the baseline (> 150 but < 200 seconds). Alternately, a continuous infusion of heparin with frequent ACT monitoring can be used to achieve the same degree of anticoagulation. Low-dose heparin protocols have been shown to reduce bleeding complications in high-risk patients when compared to regional anticoagulation with heparin and protamine neutralization. The major advantage of this technique is its simplicity. The main disadvantage is that some degree of systemic anticoagulation still occurs, necessitating careful monitoring. Also, because it involves the use of heparin, this method of anticoagulation is not suitable for patients with hehparin-induced thrombocytopenia.

TABLE 10.2 Common Standard Anticoagulation Regimens Using Unfractionated Heparin

Regimen	Advantages	Disadvantages
Initial bolus 40 IU/kg, repeated bolus 1000–2000 IU midtreatment	Ease of administration, less postdialysis bleeding	Less effective for longer dialysis times
Initial bolus 40 IU/kg, continuous infusion 10–15 IU/kg/h	Steady-state anticoagulation	May require monitoring, prolonged post dialysis bleeding
Initial bolus > 70 IU/kg, tapered continuous infusion	Steady-state anticoagulation, less postdialysis bleeding	May require monitoring, not suitable for patients with high risk of intradialytic bleeding

TABLE 10.3 Simplified Protocols Using Unfractionated Heparin (UFH) in Our Institution

UFH Protocol	Doses
Standard	Initial bolus 2000 IU
	Maintenance dose: 500 IU/h
Mini	Initial bolus 1000 IU
	Maintenance dose: 500 IU/h
Tight	Initial bolus 1000 IU units (once)
	Maintenance dose: none

Low-Molecular-Weight Heparins

Low-molecular-weight heparins (LMWHs) are derived from chemical or enzymatic depolymerization of commercial UFH and are about one-third of the molecular weight of UFH (4000 to 5000 daltons vs. mean 15,000 daltons for UFH). Like UFH, LMWHs inactivate factor Xa (see Fig. 10.1). Because LMWH molecules do not contain enough saccharide units to form the ternary complex required to simultaneously bind thrombin and antithrombin, their ability to inhibit thrombin activity is significantly less. Another important difference is that the anticoagulation effect of LMWHs is not reliably reversed by protamine sulfate. Anticoagulation monitoring also differs from UFH in that the aPTT is not accurate with LMWHs; heparinoid or anti–factor Xa activity must be measured to assess their anticoagulant activity. Currently, the recommendations are to aim for an anti-Xa activity of 0.4–0.6 IU/mL in the venous port of the extracorporeal circuit and < 0.2 IU/mL at the end of hemodialysis therapy. However, routine monitoring is typically not required and is recommended only in those patients at increased risk of bleeding.

LMWHs have been proposed to cause less bleeding and less thrombocytopenia than heparin. The LMWH dalteparin is used widely in European countries; however, the use of LMWHs for hemodialysis anticoagulation in the United States is very limited. While LMWHs have been demonstrated to be similarly safe and efficacious compared to UFH, it has generally not been found to be superior to heparin in terms of dialysis-related bleeding, and the increased cost may not justify the preferential use over UFH. It is also important to note that even though the incidence of HIT is lower than with UFH, LMWHs should not be used as a safe substitute in these patients because of the extensive cross-reactivity (> 90%) between LMWHs and standard UFH.

LMWHs can be used to decrease the thrombogenicity of the extracorporeal circuit itself by covalently coupling LMWH to all surfaces. Preliminary studies have shown that this strategy can be safely used without any additional agents, but the clinical and cost effectiveness of this approach to prevent thrombosis and bleeding compared to regional and no-heparin strategies has yet to be examined and is not readily available in outpatient dialysis units.

Recombinant Hirudin Anticoagulation

Hirudin directly binds and inhibits thrombin via the formation of a noncovalent complex (see Fig. 10.1). Recombinant hirudin (lepirudin) has been administered either as a single bolus at the start of hemodialysis or as a continuous infusion. Lepirudin is an effective anticoagulant and may result in less prolongation of the ACT than heparin. Lepirudin is primarily excreted by the kidneys, and for this reason, it should be used carefully in hemodialysis patients, as its prolonged half-life (> 35 hours) may lead to bleeding complications with repetitive use. There is no antidote available to reverse its anticoagulant effects. Lepirudin is recommended as an alternative hemodialysis anticoagulation method in patients diagnosed with HIT. It is also not readily available in outpatient dialysis units.

Argatroban

Argatroban is a direct thrombin inhibitor derived from arginine approved for the anticoagulation of the hemodialysis circuit in patients diagnosed with HIT or with other contraindications to heparin. Argatroban reversibly binds to the catalytic thrombin active site, consequently preventing fibrin formation and inhibiting activation of factors V, VIII, and XIII (see Fig. 10.1). As opposed to recombinant hirudin products, argatroban is mainly metabolized by the liver; therefore, it should be used with caution in patients with liver disease. It can be given as an initial bolus of 100–250 μg/kg followed by a maintenance infusion of 0.5–2 μg/kg/min adjusted to an aPTT 1.5–3 times of the baseline value. As with most hemodialysis anticoagulation methods, argatroban infusion should be discontinued ~ 30 minutes before the end of therapy to avoid excessive bleeding from cannulation sites. Argatroban is usually reserved for in-hospital use.

Heparinoids: Danaparoid and Fondoparinux

Heparinoids are glycosaminoglycans derived from heparin. The experience with these agents as an alternative method for hemodialysis anticoagulation is very limited. Danaparoid contains heparin sulfate, dermatan sulfate, and chondroitin sulfate. Similar to heparin, its anticoagulation effects are mainly mediated by inhibition of factor Xa (see Fig. 10.1). Danaparoid is currently not available in the United States. For monitoring, aPTT is not helpful, and anti–factor Xa activity has to be measured. There are no antidotes available. Danaparoid contains heparin-like compounds, and cross-reactivity with HIT antibodies has been reported in up to 10% of cases.

Fondoparinux is a pentasaccharide that also binds to antithrombin, causing indirect inhibition of activated factor X (see Fig. 10.1). This agent is not currently approved for hemodialysis anticoagulation, and it should be used with extreme caution in end-stage kidney disease patients since the half-life is significantly increased, which at times can lead to interdialytic systemic anticoagulation.

Regional Anticoagulation

Regional Anticoagulation With Protamine Reversal

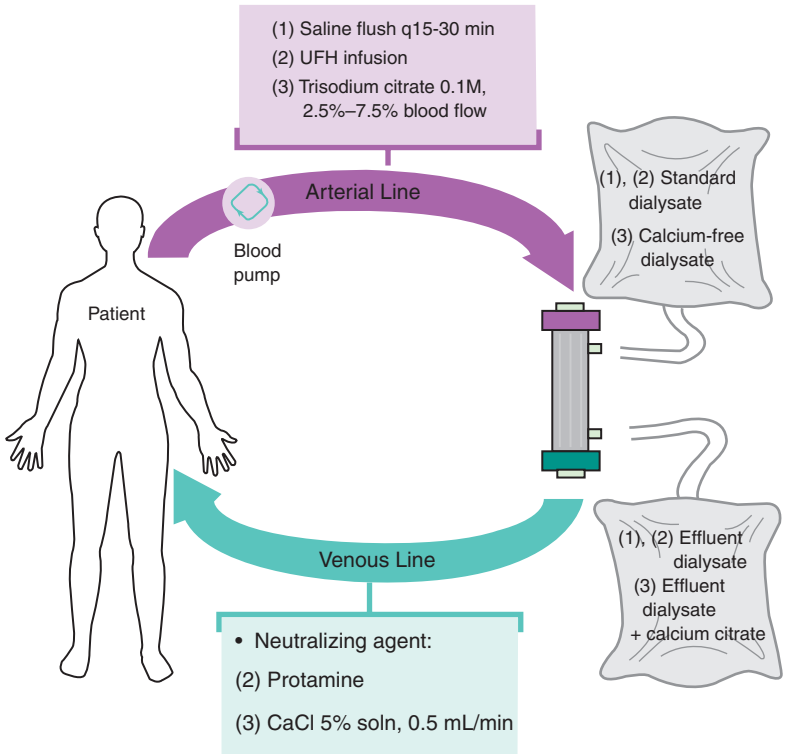
The earliest method described to reduce hemodialysis-associated bleeding was regional anticoagulation with protamine reversal. This procedure involves the constant infusion of heparin into the dialyzer arterial line (predialyzer),

and the simultaneous constant infusion of the neutralizing agent, protamine, into the venous (post-dialyzer) limb of the circuit to prevent systemic anticoagulation (Fig. 10.2). The infusion pump rates are adjusted to keep the whole blood ACT in the dialyzer circuit at 250 seconds and the blood returning to the patient at its predialysis baseline. Because of the technical difficulties and the release of free heparin from the protamine-heparin complex back into the general circulation 2 to 4 hours after the termination of dialysis (resulting in rebound bleeding), protamine reversal has been largely abandoned. In addition, simpler regimens consisting of minimum and no dose heparin as well as citrate regional anticoagulation have subsequently been developed that offer a lower incidence of bleeding complications.

Regional Citrate Anticoagulation

The regional citrate regimen that has been adopted in many institutions involves the continuous infusion of isosmotic trisodium citrate solution (102 mmol/L) into the arterial limb of the dialyzer. Citrate chelates calcium is a key cofactor required for different steps in the coagulation cascade (see Fig. 10.1). The fall in the free plasma calcium concentration induced by binding to citrate prevents the progression of the coagulation cascade in the extracorporeal circuit. A calcium-free dialysate is used and some of the citrate-calcium complex is then removed across the dialyzer. The citrate infusion rate is adjusted to keep the ACT above 200 seconds in the arterial limb. Normocalcemia and regional anticoagulation is achieved by the infusion of 5% calcium chloride into the venous return line at a rate of 0.5 mL/min. This rate is constantly adjusted according to frequent measurements of plasma-calcium concentration to prevent hypocalcemia or hypercalcemia. A modification of this technique utilizes hypertonic trisodium citrate (1.6 mol/L) and dialysate containing 3 mEq/L of calcium in an attempt to minimize the amounts of replacement calcium needed via venous infusion (see Fig. 10.2). Citrate is converted to bicarbonate in the liver, which may lead to metabolic alkalosis, especially when used with CRRT. For this reason, it is recommended to use a dialysate with a lower concentration of bicarbonate. At times, the metabolic alkalosis is severe enough to require treatment with a hydrochloric acid infusion.

Comparative trials have shown a reduced incidence of bleeding with citrate-based regimens compared to standard heparin protocols, so it is recommended as an alternative method for patients with high bleeding risk. Apart from technical complexity and the intensity of monitoring, the major problems with regional citrate anticoagulation are the possibility of hypocalcemia, hypercalcemia, hypernatremia (due to the hypertonic sodium citrate solution), and metabolic alkalosis (due to bicarbonate generated during hepatic metabolism of citrate). Patients with liver insufficiency are especially at risk for metabolic complications. Citrate



• **Fig. 10.2** Schematic Representation of Hemodialysis Anticoagulation Modalities for Patients at Increased Risk of Bleeding. The modalities depicted are (1) no heparin/saline flush; (2) regional heparin anticoagulation with protamine reversal; and (3) regional citrate anticoagulation.

infusion can also affect the function of cellular elements of the blood, including leukocyte activation and platelet function via its hypocalcemic effects. If closely monitored, however, the complication rate is relatively low. It is mostly reserved for in-hospital use.

Prostacyclin Regional Anticoagulation

The arachidonic metabolite prostacyclin is a vasodilator and inhibitor of platelet aggregation. Its in vitro half-life is 3 to 5 minutes due to rapid metabolism by endothelial-smooth muscle. Prostacyclin regional anticoagulation involves the infusion of prostacyclin into the dialyzer circuit at 4 to 8 ng/kg per minute. This method is rarely recommended due to its unfavorable side-effect profile, including headache, lightheadedness, facial flushing, hypotension due to vasodilation, and cost.

Nafamostat is a prostacyclin analog associated with fewer adverse effects on blood pressure but is not yet available in the United States. It may, however, be associated with an unacceptably high incidence of clot formation. In one study using nafamostat, clot formation was observed in up to 36% of dialyzers despite adequate prolongation of the aPTT. In addition, nafamostat cannot be used with polyacrylonitrile membranes due to adsorption onto the membrane surface.

Anticoagulant-Free Dialysis

Heparin-Free Dialysis

In circumstances where patients are at increased risk of bleeding, the use of anticoagulation becomes challenging during hemodialysis. A number of alternative modalities have been used in these at-risk patients, such as low-dose heparin or regional anticoagulation. However, there is still an associated risk of bleeding with these strategies, which can be as high as 50%. The use of regional citrate anticoagulation is generally restricted to inpatient units or specifically designated outpatient units. Therefore, in patients with increased bleeding risk or active bleeding, no-heparin hemodialysis is the preferred method of anticoagulation. This is also a reasonable alternative for patients with HIT or other contraindications to heparin. In this protocol, the dialyzer and tubing are pretreated with 2000 to 5000 IU of heparin contained in 1 L of normal saline or, alternatively (especially in HIT patients), just saline. In the case of heparinized saline pretreatment, the extracorporeal circuit is flushed with saline alone prior to the start of the dialysis treatment so that heparin is not administered to the patient. Extracorporeal blood flows are rapidly increased to 250–500 mL/min and maintained throughout the treatment with 25 to 30 mL saline flushes administered every 15 to 30 minutes into the arterial (predialyzer) limb to minimize hemoconcentration and to wash fibrin strands from the dialyzer into the bubble trap. Of note, the volume of saline administered must be added to the ultrafiltration goal during dialysis to prevent volume overload. One-on-one nursing is required for administration of saline flushes and careful monitoring of the arterial and venous pressure alarms to detect early extracorporeal circuit clotting.

Using this technique, about 90% of intensive care unit (ICU) patients with increased risk of bleeding who require hemodialysis can be successfully dialyzed with only a 2% clotting rate in the extracorporeal circuit. No significant loss of clearances has been reported compared to patients on standard anticoagulation. In approximately 5% of the cases, conversion to minimum-dose heparin or treatment discontinuation is required.

The disadvantages of this technique include the associated increased ultrafiltration rate required to maintain volume status, which can promote hypotension and increase dialyzer circuit clotting and thrombosis. An additional problem with the no-heparin technique is that blood transfusions cannot usually be given through the dialyzer circuit due to the increased risk of clotting, which may pose difficulty for patients with limited peripheral access. A potential solution, which has been successfully used, is to utilize a large-bore stopcock to transfuse blood into the venous limb (postdialyzer) of the circuit. Another disadvantage is the increased staff time needed for close observation, which can potentially elevate dialysis costs. For these reasons, no-heparin strategies are not recommended as a long-term anticoagulation therapy for outpatient hemodialysis.

Heparin-Grafted Dialyzer

Another alternative to no-heparin hemodialysis is the use of heparin-grafted dialyzers, which have been successfully used alone (without saline flushes) or in combination with a citrate-enriched dialysate. These dialyzers are coated with a substance that binds heparin. The clotting rate associated with these dialyzers seems to be between 15% and 30%. Preliminary studies suggest that heparin-grafted dialyzers are noninferior to current standard heparin-free dialysis, are easy to use, and represent a reasonable choice for hemodialysis anticoagulation in patients with high bleeding risk but are not readily available.

Citrate Dialysate

Similar to regional citrate anticoagulation, this strategy utilizes the calcium inhibiting effects of citrate to block different steps in the coagulation cascade (see Fig. 10.1). The citrate-enriched dialysate replaces the acetate normally used for acidification, utilizing citric acid at a relatively low concentration (2.4 mEq/L, 0.8 mmol/L). This results in reduced clot formation locally in the extracorporeal circuit, allowing a dialysis treatment with either

no or only a very low dose of heparin for anticoagulation. Importantly, citrate dialysate lowers serum calcium sufficiently to interfere with the clotting cascade, but not enough to cause symptomatic hypocalcemia. Thus, calcium replacement is not necessary, as opposed to regional citrate anticoagulation.

Heparin-Induced Thrombocytopenia

UFH can cause a modest reduction in platelet count (< 100,000/mL), which is usually reversible (heparin-induced thrombocytopenia type I). In approximately 5%–10% of the patients treated with heparin, there is an immunologic reaction characterized by the formation of antibodies against the complex of heparin and platelet factor 4. This leads to platelet activation and consumption, leading to severe thrombocytopenia (usually 30%–50% below baseline), known as HIT type II. The main clinical concern in this disorder is a high incidence of arterial and venous thrombosis rather than bleeding. Given the overall safety and reasonable ease of use, no-heparin hemodialysis should be the first option among those with HIT. If heparin-free dialysis cannot be performed, then the patient should be anticoagulated with regional citrate or, in certain situations, even converted to peritoneal dialysis. Another option would be the administration of one of the three drugs that appear to be effective in patients with HIT: danaparoid, recombinant hirudin (lepirudin), and argatroban. Melagatran is a novel long-acting direct thrombin inhibitor, which is currently available only in Europe. Feasibility studies using these agents have been conducted in hemodialysis patients, and they appear to be effective in preventing thrombosis without excess bleeding risk. However, there is no published experience concerning their use in patients with HIT. Overall, the experience with these drugs is limited.

Importantly, as long as the platelet count remains low in HIT and there is clinical evidence of active disease, systemic (and not regional) anticoagulation is mandatory. Table 10.4 summarizes the recommendations for use of these agents based on currently available data.

Catheter Lock in Patients With HIT

Hemodialysis catheter lock options in patients with HIT are to pressure bag the catheters (which is impractical for outpatients) or instill either tissue plasminogen activator or urokinase. Highly concentrated (47%) citrate has also been used but is not Food and Drug Administration approved due to issues of accidental systemic injection with resulting arrhythmias. Studies with lower concentration citrate solutions (4% to 7%) indicate that this strategy is safe and similarly effective for the maintenance of long-term interdialytic patency of hemodialysis catheters. A study using a 30% citrate locking solution found no increase in adverse events and also found a decreased risk of catheter-related bacteremia compared to a standard heparin locking solution.

TABLE 10.4 Anticoagulation for Dialysis-Dependent Patients With HIT

Parameter	Danaparoid	Lepirudin	Argatroban[a]	Melagatran
Hemodialysis				
Bolus therapy	3750 anti-FXa U bolus prior to the first two HD treatments, then dose adjust using levels[d]	0.15 mg/kg bolus prior to HD	0.1 mg/kg bolus prior to HD	Bolus IV dose of 2 mg, add to dialysis fluid for concentration of 0.2 mg/L
Infusion therapy	–	–	0.1–0.2 mg/kg/h	ND
Monitoring test	Anti–factor Xa level	aPTT	aPTT	aPTT
Target result[b]	0.0–0.4 anti–FXa units pre-HD	2.0–2.5× mean of the normal pool	1.5–3.0× mean of the normal pool	ND
Catheter lock				
Concentration/ volume	750 U in 50 mL saline, then 5–10 mL per port	5 mg/mL per port[c]	ND	ND

aPTT, Activated partial thromboplastin time; *HD*, hemodialysis; *HIT*, heparin-induced thrombocytopenia; *ND*, no data available at this time.
[a]Argatroban should not be administered without first verifying normal liver function. The dose needs to be adjusted for hepatic insufficiency.
[b]Target results for the aPTTs are based on individual coagulation laboratory mean values. Do not exceed 100 seconds.
[c]Must be aspirated prior to hemodialysis.
[d]Use lower bolus dosing if weight is < 50 kg.
Modified from O'Shea SI, Ortel TL, Kovalik EC. Heparin-induced thrombocytopenia in dialysis: alternative methods of anticoagulation for dialysis-dependent patients with heparin-induced thrombocytopenia. *Semin Dial*. 2003;16:61-67.

Recommended Reading

Daugirdas JT, Bernardo AA. Hemodialysis effect on platelet count and function and hemodialysis-associated thrombocytopenia. *Kidney International.* 2012;82:147–157.

Comprehensive review summarizing the effects of hemodialysis on platelets function; case reports and one large series of severe thrombocytopenia.

Davenport A. What are the anticoagulation options for intermittent hemodialysis? *Nat Rev Nephrol.* 2011;7:499–508.

Comprehensive review of different anticoagulant agents used for hemodialysis.

Fischer KG. Essentials of anticoagulation in hemodialysis. *Hemodialysis International.* 2007;11:178–189.

A comprehensive review of basic principle of coagulation cascade, hemostatic abnormalities in dialysis patients and principles of anticoagulation and available agents used in routine hemodialysis.

Frank R, Muller U, Lanzmich R, et al. Anticoagulant-free Genius hemodialysis using low molecular weight heparin–coated circuits. *Nephrol Dial Transplant.* 2006;21:1013.

Description of a novel anticoagulation modality using LMW heparin covalently bonded to dialyzer circuits.

Laville M, Dorval M, et al. Results of the HepZero study comparing heparin-grafted membrane and standard care show that heparin-grafted dialyzer is safe and easy to use for heparin-free dialysis. *Kidney International.* 2014;86:1260–1267.

A large, randomized, multicenter, international controlled open-label trial comparing no-heparin hemodialysis strategies vs heparin grafted dialyzer. The study showed that heparin-grafted membranes are not inferior, safe, and easy to use method for non-heparin dialysis.

Lim W, Cook DJ, Crowther MA. Safety and efficacy of low molecular weight heparins for hemodialysis in patients with end-stage kidney failure: a meta-analysis of randomized trials. *J Am Soc Nephrol.* 2004;15:3192.

Meta-analysis of 11 clinical trials comparing LMW heparin with other anticoagulant strategies. There was no increased risk of bleeding or circuit thrombosis compared to UFH.

Morabito S, Pistolesi V, et al. Regional citrate anticoagulation for RRTs in critically ill patients with AKI. *Clin J Am Soc Nephrol.* 2014;9:2173–2188.

In-depth review of the use of regional citrate anticoagulation in patients undergoing hemodialysis for acute kidney injury, citrate pharmacokinetics, and future perspectives for simplification of RCA protocols.

O'Shea SI, Ortel TL, Kovalik EC. Alternate methods of anticoagulation for dialysis-dependent patients with heparin-induced thrombocytopenia. *Semin Dial.* 2003;16(1):61–67.

Review of the prevalence, diagnosis, and treatment data regarding HIT.

Shen JI, Winkelmayer WC. Use and safety of unfractionated heparin for anticoagulation during maintenance hemodialysis. *Am J Kidney Dis.* 2012;60(3):473–486.

Case presentation and comprehensive review of different anticoagulation strategies for hemodialysis, with emphasis on heparin, its pharmacology, dosage, and complications.

Weijmer MC, Van den Dorpel MA, Van de Ven PG, et al. Randomized, clinical trial comparison of trisodium citrate 30 percent and heparin as catheter-locking solution in hemodialysis patients. *Am J Kidney Dis.* 2005;2769:2777.

This prospective study found that the use of a trisodium citrate catheter locking solution reduced the incidence of catheter related bacteremia and was not associated with any untoward metabolic consequences compared to standard heparin lock.

Wu MY, Hsu YH, Bai CH, et al. Regional citrate versus heparin anticoagulation for continuous kidney replacement therapy: a meta-analysis of randomized controlled trials. *Am J Kidney Dis.* 2012;59(6):810–818.

Systematic review and meta-analysis of six randomized control trials comparing regional citrate versus heparin for CRRT anticoagulation. There was lower bleeding risk with the use of citrate, but no difference on efficacy compared to UFH.

Lazrak HH, René É, Elftouh N, Leblanc M, Lafrance JP. Safety of low-molecular-weight heparin compared to unfractionated heparin in hemodialysis: a systematic review and meta-analysis. *BMC Nephrol.* 2017 Jun 7;18(1):187.

Systematic review of 17 studies evaluating the safety of LMWH compared to UFH as an anticoagulant for chronic hemodialysis.

11

Common Clinical Problems in Hemodialysis

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Introduction

Hemodialysis (HD) treatments are performed millions of times per year and offer a life-saving and life-sustaining therapy. Technological advances in the delivery of HD have occurred over the past 70 years and these have been supplemented with enhanced patient monitoring and the development of protocols and procedures that govern the operation of HD facilities.[1] Despite these advances, complications of HD still occur, and clinicians must be able to rapidly recognize and react appropriately to these problems.[2]

Investigating an Adverse Event on Hemodialysis

All adverse events occurring during a dialysis session require thorough, stepwise, and multidisciplinary investigation. Root cause analyses (RCAs) seek to identify the origins of a problem through a rigorous set of tools. RCAs may identify (1) physical causes where a material or machine failed, (2) human causes where people did not follow procedures, and (3) organizational causes where systems, processes, or policies are faulty. Each dialysis facility should have an RCA team that is readily available to review incidents and should develop reports with the aim of preventing similar incidents.

Acute Reactions During Hemodialysis

Adverse reactions during an HD treatment may be caused by exposure of blood to surface components of the extracorporeal circuit, including the dialyzer, tubing, and other compounds used in the manufacturing and sterilization processes. These adverse reactions can range in severity from mild to life-threatening anaphylactic or anaphylactoid reactions.[3,4]

The pattern and timing of the reaction give clues as to the etiology. For example, symptoms occurring within the first 5 minutes after starting HD point toward issues with the dialyzer, tubing, or dialysate. Typical allergic-like symptoms may be unusual in end-stage kidney disease (ESKD) patients, and new symptoms arising during treatment should prompt consideration of an HD-related reaction.

Reactions Associated With the Dialysis Circuit

Allergic reactions occurring during dialysis are best classified by timing and severity: type A reactions occur within the first 5 to 20 minutes of the HD session with typical anaphylaxis-type symptoms, while type B reactions occur later in the session with milder symptoms.[5] Type A reactions are likely immunoglobulin E (IgE)–mediated, while type B reactions are anaphylactoid and may be related to activation of the complement cascade.[5] In the past, reactions to the dialysis membrane or sterilization technique were common, but most U.S. dialysis facilities now utilize synthetic biocompatible membranes (composed of polymethylmethacrylate, polyethersulfone, polysulfone, or polyacrylonitrile [PAN]), which are irradiated and have a lower risk of reactions.[6] A current reaction of interest is with the use of PAN.[7] In the 1990s, severe anaphylactoid reactions were reported in patients dialyzed with PAN membranes who were taking angiotensin-converting enzyme (ACE) inhibitors.[8] The interaction between the use of ACE inhibitors and PAN membranes may be related to significant increases in bradykinin levels.[9] It is recommended that ACE inhibitors be stopped at least 24 hours prior to the use of a PAN membrane or that alternative dialyzers be utilized.

Rare reactions to dialysis membranes of the polyarylsulfone family (polysulfone, polyethersulfone) have been reported.[10] An analysis of these reactions could not isolate the sterilization method, housing materials, or potting materials as etiologies. Importantly, 85% of these patients also reacted to other dialysis membranes of the same chemical family, and thus, the use of alternative membranes (PAN, substituted cellulose, or polymethylmethacrylate) is needed for these patients.

Reactions Associated With Drugs and Other Exposures

During a dialysis session, patients receive several medications (heparin, erythropoietin, iron compounds), as well as drugs given sporadically for specific indications (antibiotics). Patients can develop reactions to these medications, and a review of medication administration is required for all patients developing a reaction.

There are reports of heparin-induced thrombocytopenia (HIT)-associated anaphylactoid reactions in HD patients occurring 5–30 minutes after intravenous (IV) or subcutaneous administration of either unfractionated heparin (UFH) or low-molecular-weight heparins (LWMH).[11] Clinical features include abrupt falls in platelet counts (consistent with HIT), hypotension or hypertension, wheezing, dyspnea, and cardiovascular collapse. These patients have been found to have anti–platelet factor (PF)-4/heparin antibodies. In addition, both UFH and LWMH have been linked to episodes of typical anaphylaxis during HD.[12,13] Heparin "allergy" in an HD patient may also be caused by preservatives in the heparin preparation such as paraoxybenzoic esters.[14]

IV iron compounds administered during HD can be associated with a range of adverse reactions, including severe, life-threatening events. The prevalence of hypersensitivity reactions to IV iron preparations is very low (0.01% to 0.1%). IV iron reactions do not appear to be IgE mediated and are likely nonimmune in nature.[15] These reactions can range from minor symptoms such as pruritus, flushing, arthralgias, and myalgias to more significant symptoms such as chest pain, persistent hypotension, shortness of breath, and cardiovascular collapse.[16]

Approach to the Dialysis Patient With a Reaction

A rapid assessment of the patient, as well as a review of the dialysis session, including the medications administered, is a critical first step in responding to a patient reaction. The dialysis procedure should be halted immediately, and blood should not be returned to the patient. Dialysis-related factors such as hemolysis, air embolism, or a pyrogenic reaction should be assessed (see later) before determining that the patient may be suffering from either a dialyzer- or medication-related event. For those patients with signs and symptoms of anaphylaxis, rapid administration of subcutaneous epinephrine, IV corticosteroids, and antihistamines (H_1 and H_2 antagonists) should occur, along with respiratory support if needed.

Reactions Associated With Microbiological Contamination

Naturally occurring water bacteria commonly found in HD water systems include gram-negative bacteria (GNB) and nontuberculous mycobacteria. GNB releases endotoxin or lipopolysaccharide (LPS) and other bacterial products.[17] The accepted standards for water purity are those recommended by the Association for the Advancement of Medical Instrumentation (AAMI) and the European Pharmacopeia, which respectively allow bacterial growth of <200 and <100 colony-forming facilities (CFU)/mL and an endotoxin concentration of <2 and <0.25 IU/mL.

Outbreaks of clusters of infection in HD patients have been ascribed to bacterial contamination that can occur at multiple places along the HD circuit, including the dialysate (bicarbonate solutions are potentially at risk for contamination), carbon filters, inadequate disinfection, and other sources. The passage of endotoxin from the dialysate into the blood can occur by diffusion or convection. High-flux dialyzers increase the risk of passage of endotoxin, particularly lipid A (~ 2000 Da), the active moiety of LPS, from dialysate into blood. This may cause a transient febrile reaction associated with rigors and hypotension. In these cases, careful examination of the dialysis access is warranted, and blood cultures should be obtained. An outbreak of bacteremia among several patients involving a similar organism should prompt a thorough search for bacterial contaminants of the dialysis equipment and water treatment units.

Neurologic and Muscular Complications

Neurological and muscular complications are commonly encountered in patients undergoing HD.

Muscle Cramps

Muscle cramps are defined as prolonged and painful involuntary skeletal muscle contractions and are a common occurrence that has been reported in as many as 33% to 86% of HD treatments.[18] There is little research to guide our understanding of the pathophysiology, therapy, and prevention of muscle cramps. Muscle cramps typically occur near the end of the HD session and most often involve the muscles of the lower extremity. Lower dialysate sodium levels and higher ultrafiltration rates appear to be risk factors.[18]

Acute management often includes transiently slowing or stopping ultrafiltration as well as intradialytic massage and stretching of the affected muscle groups.[19–21]. For those patients who develop hypotension along with muscle cramps, prompt attention to raising blood pressure (BP) (slowing or stopping ultrafiltration, slowing blood flow rate, placing the patient in Trendelenburg position, and even midodrine) should be the first course of action.

Several strategies have shown variable efficacy in the prevention of muscle cramps. For patients who seem to develop muscle cramps associated with the need for high ultrafiltration rates (such as greater than 10–13 mL/kg/h), minimizing interdialytic weight gains is critical but often difficult to achieve. The length of the HD session could also be increased. Minimizing episodes of intradialytic hypotension (IDH) and the use of sodium modeling may also

be effective in some patients.[22] It also may be reasonable to empirically increase the target weight by 0.5 kg to see if this lowers the frequency of muscle cramps. While controversial, L-carnitine supplementation (administered intravenously [20 mg/kg] after HD or orally [330 mg two to three times per day]) in those patients with low levels may decrease the frequency of muscle cramps.[23] Vitamin E supplementation has also shown variable efficacy.[24] There are very limited data on a variety of other therapies, including the use of gabapentin, short-acting benzodiazepines, and phenytoin.[22]

Headache

Headache is a common complaint in HD patients occurring with an incidence ranging from 27% to 73%.[25–28] It is often transient and, by definition, resolves within 48–72 hours after dialysis.[26] Patients who develop a headache may have lower magnesium levels in both predialysis and postdialysis, greater intradialytic decreases in serum urea levels, larger changes in body weight during HD sessions, and higher predialysis systolic and diastolic BPs.[25–28] Headache may be a mild form of the dialysis disequilibrium syndrome (DDS) (discussed later).[29] Headache may also be a somatic complaint seen in patients with depression.[30] General management principles are followed in the treatment of headaches: oral analgesics (acetaminophen), magnesium supplementation for those patients with low levels, avoidance of large BP and weight changes, and avoidance of caffeine over-usage.

Dialysis Disequilibrium Syndrome

DDS is defined as neurological deterioration occurring during HD and more typically occurring in patients during or immediately after their first treatment.[31–35] Risk factors include high predialysis blood urea nitrogen levels (> 175 mg/dL), a rapid fall in blood urea nitrogen levels during HD, preexisting neurological conditions, hyponatremia, and liver disease.[31–35] The symptoms mimic those occurring with increased intracranial pressure, such as restlessness, headache, nausea, vomiting, hypertension, mental confusion, obtundation, seizures, and coma.[31–35] Brain imaging (either computed tomography or magnetic resonance imaging) may reveal cerebral edema in patients with DDS. The primary pathophysiology is the development of cerebral edema and increased intracranial pressure driven by water movement into brain cells and the interstitium by an osmotic gradient that develops as serum urea and other effective osmoles are removed by dialysis ("reverse urea hypothesis").[34,35]

Prevention of DDS focuses on minimizing the osmotic gradient that leads to water entering the central nervous system (CNS). Thus, a reduction in the blood urea concentration by 40% (urea reduction ratio of 0.4) should be a maximum during a first HD treatment.[36] The first HD session should be limited to 2 to 2.5 hours in duration, and the blood flow should be 200 to 250 mL/h to achieve this goal. For those at the highest risk for DDS (such as those with acute kidney injury and traumatic brain injury or an intracranial hemorrhage), continuous renal replacement therapy with slow urea removal should be considered. Another strategy used to prevent DDS is to raise the osmolality of the intravascular compartment during HD. This decreases the osmotic gradient and lowers the risk of cerebral edema. The easiest way to achieve this is to increase the concentration of sodium in the dialysate and utilize sodium modeling techniques.[36] Other osmotic agents such as mannitol and glucose have also been successfully utilized in the prevention of DDS.[36] Treatment of DDS, once established, relies on rapidly reducing intracranial pressure by raising blood osmolality with mannitol or hypertonic saline.[36]

Restless Legs Syndrome

Restless legs syndrome (RLS) is characterized by an uncomfortable and urgent need to move the limbs (usually the lower extremities) and typically begins or worsens during periods of rest or inactivity.[37–40] ESKD patients have a much higher prevalence rate (approximately 30%) of RLS than the general population. RLS can manifest itself during the HD session, and up to 20% of patients undergoing HD prematurely terminate a dialysis session secondary to the sensory and motor symptoms of RLS. In addition, studies have demonstrated that RLS negatively impacts the quality of life for HD patients with negative effects on sleep quality and quantity with a higher prevalence of depression and anxiety.[41,42]

Treatment of RLS in ESKD patients is challenging. The first-line pharmacological therapy for RLS is a dopamine agonist such as ropinirole or pramipexole. There are several small trials showing that these agents can decrease RLS symptoms by approximately 70%.[43,44] The side effects of these agents can include nausea, vomiting, and nightmares. The anticonvulsant gabapentin has also shown efficacy and is approved by the Food and Drug Administration for the treatment of RLS.[45]

Seizures

There are numerous etiologies of seizures in the patient undergoing dialysis. It is important to know the patient's history, medication use, and details of the dialysis session, as this will often yield significant clues as to the cause of the seizure. A rapid physical examination looking for any focal neurologic deficits should be performed as this may suggest an intracranial process (such as a stroke or subdural hematoma). Patients who are initiating HD may develop a seizure due to DDS or from severe electrolyte disturbances such as hyponatremia or hypocalcemia.[46] Erythropoietin, especially in higher doses, had been associated with the development of hypertensive encephalopathy and seizures in as many as 2% to 17% of patients.[47] However, the contemporary uses of much lower doses of erythropoietin as well as more aggressive control of BP have made erythropoietin-associated seizures an uncommon occurrence.[47,48]

Patients with a history of seizures and taking chronic antiepileptic medications pose special challenges in the HD facility. ESKD and HD alter the distribution, metabolism, and clearance of many antiepileptic drugs.[49] Some medications such as levetiracetam, phenobarbital, and primidone are removed by dialysis and thus require supplementation or careful timing of administration to avoid lowering therapeutic levels and precipitating "breakthrough" seizures.[49] Other drugs such as phenytoin, carbamazepine, and sodium valproate are poorly dialyzed and do not require supplementation. In all cases, antiepileptic drug levels should be followed closely and support from pharmacists should be sought.

Treatment of established seizures requires cessation of dialysis, maintenance of airway patency, and investigation for metabolic abnormalities. IV diazepam or clonazepam and phenytoin may be required. IV administration of 50% dextrose in water should be administered if hypoglycemia is suspected.

Other Neurological Complications

Visual loss is rare during HD and may be caused by central retinal vein occlusion, precipitation of acute glaucoma (due to changes in osmolality), ischemic optic neuropathy associated with IDH, or Purtscher-like retinopathy caused by leukoembolization.[50] Patients experiencing visual changes during HD should have their treatment stopped immediately and be referred for an emergent ophthalmology examination.

Cardiovascular Complications

Intradialytic Hypotension

IDH is a frequent event, occurring during up to 20% of dialysis sessions.[51] Estimates of frequency vary as no agreed-upon definition exists. Authors have variably defined IDH as a drop in mean arterial or systolic BP below a certain threshold or an event leading to symptoms requiring clinical intervention. A recent Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference suggested a pragmatic approach: "Any symptomatic decrease in BP or a nadir intradialytic SBP < 90 mmHg should prompt reassessment of BP and volume management."[52] Regardless of definition, the pathophysiology remains complex involving interplay of several factors: ultrafiltration rate, vascular "refill" rate, osmolar changes and fluid shifts, changes in compensatory mechanisms such as impaired baroreceptor reflexes, and underlying pathology such as heart failure.

Several factors have been suggested to predispose to IDH: long interdialytic break, short treatment times, longer dialysis vintage, and higher ultrafiltration rates, among others. Importantly, IDH has been associated with several negative health outcomes—recurrent cardiac stunning and remodeling, access thrombosis, and increased 1- and 5-year mortality.[53,54] Patients also may suffer a number of symptoms with IDH, including postdialysis fatigue, cramping, nausea, and dizziness.[55] Treatment-related interventions include utilization of cooler dialysate, linear sodium modeling (without net sodium transfer), and limitation of ultrafiltration rates. Medication-related strategies include continuation of diuretics after the onset of dialysis dependence and use of the alpha-1 receptor agonist midodrine, which has been found safe, although with variable efficacy.[56,57] Dietary counseling regarding sodium and fluid intake is the cornerstone of counseling to reduce interdialytic weight gain.

Intradialytic Hypertension

Intradialytic hypertension occurs less frequently than hypotension, complicating an estimated 5%–15% of sessions.[58] Definitions here too vary, but the most current definition is a sustained rise of 10 mm Hg or more in the systolic BP from the beginning to end of the dialysis session.[52] Paradoxically, high BPs had been associated with a survival advantage; however, analysis of 24-hour ambulatory BP and home monitors shows the more typical pattern of increased mortality at extremes of high BP.[59]

The pathophysiology of intradialytic hypertension is poorly understood but many factors may play a role, including sodium and volume overload, stimulation of the renin–angiotensin–aldosterone system, enhanced sympathetic tone, endothelial cell dysfunction, and decreased vascular compliance. Treatment strategies should be individualized to the most likely mechanism. As in hypotension, intensive dietary support to reduce sodium and fluid intake should be employed, which will facilitate gentle probing of target weight. This strategy yielded significant reductions in BP in the Dry-weight Reduction in Hypertensive Hemodialysis Patients (DRIP) trial, although BP improvements benefits may be delayed.[60] Converting to less dialyzable antihypertensive medications may also be useful. Short daily dialysis has been shown to reduce predialysis and postdialysis systolic measurements by ~ 10 mm Hg, although this strategy may be limited by practical or logistical considerations.[61] A role for mineralocorticoid antagonists remains under investigation, with two large trials underway and the published SPIN-D trial demonstrating a good safety profile for spironolactone in dialysis patients at doses under 50 mg.[62]

Arrhythmias and Sudden Cardiac Death

Lethal arrhythmias and cardiac arrest are the leading cause of death for dialysis patients—accounting for almost one-third of mortality.[63] The overall prevalence of atrial fibrillation is estimated at approximately 20% in U.S. Renal Data System (USRDS) data, with ventricular arrhythmias just under 5%. Determining the true nature and frequency of arrhythmias has been hampered by a lack of large trials and the difficulties of longer-term cardiac rhythm monitoring.

More recently, implantable loop recorders (ILRs) have become available and used to evaluate small cohorts of dialysis patients. Three studies have separately shown a

high prevalence of arrhythmias in a diversity of dialysis patients.[64–66] Unsurprisingly, atrial arrhythmias/supraventricular tachycardias predominate, occurring in ~90% of patients, although these were less often clinically significant. Temporal patterns were seen in at least one study and demonstrated the highest rates of atrial arrhythmias occurring during the first dialysis session following the long interdialytic break.[66] The highest rates of clinically significant bradyarrhythmias occurred in the final 12 hours of the long interdialytic break preceding dialysis. Fatal arrhythmias were rare, but the most common were bradycardia and asystole, not the expected ventricular tachycardias or fibrillation. If this finding is generalizable to larger dialysis populations, it may explain the lack of benefit seen in prophylactic implantation of implantable cardiac defibrillators.

The underlying cause of the high arrhythmia burden in dialysis patients remains unclear and is most likely multifactorial in nature. Patient factors may include high underlying rates of coronary artery disease, structural and valvular heart disease, high prevalence of prolonged Qt intervals, and electrolyte and fluid imbalances developed over the interdialytic period. Procedural factors include rapid volume and electrolyte shifts as well as dialysis-induced transient myocardial stunning. In one of the previously noted studies, higher predialysis calcium and magnesium were associated with lower arrhythmia rates, while rapid volume and potassium removal were associated with increased frequency.[67]

Acute Vascular Access Complications

Access Hemorrhage

Access hemorrhage, typically a ruptured pseudoaneurysm in an arteriovenous fistula (AVF), is a rare but potentially life-threatening complication requiring rapid intervention. This is due to the inherent risk from high AVF blood flow rate, which may exceed 1 L/min. Estimates of prevalence of serious or fatal access hemorrhage suffer from a lack of reliable data, but one review of Medicare data suggests that it was the cause of death in 0.4% of dialysis patients.[68] AVF rupture is more common at home, but 1%–19% of these events may occur in the facility.[69] Contributing factors may be lack of site rotation during cannulation leading to aneurysm formation, infected buttonhole sites, and increased back pressure from proximal stenoses. Preventive strategies include a thorough examination of the access by familiar personnel to identify signs of thinning of the skin/aneurysmal dilatation or evidence of sentinel bleeding and/or ulceration. In the event of a rupture, immediate direct pressure is required, given the potential for exsanguination. Patients should be hospitalized with rapid vascular surgery or interventional radiology intervention. Despite the catastrophic nature of an access hemorrhage, many can be salvaged through open surgical or endovascular repairs.[70]

Access Thrombosis

Access thrombosis is a familiar and frustrating complication for providers and patients alike. It is also a leading cause of secondary access failure. Details related to thrombosis, such as access surveillance programs and details of pathophysiology, are covered in detail elsewhere in this text. Access thrombosis is most commonly encountered during the predialysis exam but may also occur during treatment. The most important steps for the facility team are to organize intervention—most typically percutaneous thrombectomy or "declot," although open surgical interventions may be appropriate as well. The optimal timing from diagnosis to thrombectomy is unknown, but generally, earlier is thought to have better outcomes. Early intervention also reduces the risk a patient will require a central venous catheter for dialysis while awaiting thrombectomy. The most recent KDOQI vascular access guidelines do not recommend a specific timing or method of declot but reference superior outcomes of intervention occurring <6 hours from diagnosis.[71] Postthrombectomy outcomes in the short-term are generally good; however, access teams must provide continued scrutiny as rethrombosis is a frequent event and long-term patency rates drop markedly at 3 months postintervention.[72]

Hematologic Complications

Commonly noted hematological complications include dialysis-induced leukopenia, hemolysis, and thrombocytopenia. Of these, dialysis-induced leukopenia is the least significant. Originally described in the 1970s, leukopenia was thought to be due to sequestration of granulocytes into the pulmonary vasculature triggered by complement activation.[73] This phenomenon was more often associated with cellulose dialyzers, although it has been described with polysulfone. It is usually transient and self-limited.

Dialysis-Associated Hemolysis

Dialysis-associated hemolysis (DAH) is defined as clinically significant hemolysis that occurs during or as a consequence of the dialysis procedure. Despite safety improvements, DAH still occurs and can be fatal. Causes can be broadly broken into mechanical/machine related or dialysate composition/impurity related hemolysis. Major causes of mechanical-related hemolysis include small gauge needles, kinked tubing, and malfunctioning blood warmers with dramatically elevated temperatures.[74,75] More common is contamination of the dialysate itself. Chloramines used to disinfect municipal water supplies are the most frequently noted cause. This may occur due to overload of the carbon tanks when water supplies are treated with large boluses or simply saturation or failure of the tanks themselves. A number of other contaminants such as trace minerals from plumbing supplies, cleaning products from water loop sterilization, or nitrites/nitrates from agricultural production have also been reported to cause hemolysis. Finally,

hypotonic dialysate in conjunction with failed conductivity meters have also lead to dangerous hemolysis.

Clinical symptoms may range as mild as perceived erythropoietin stimulating agent resistance to frank hypoxia; chest, back, and abdominal pain; and nausea and vomiting. Hemolysis and methemoglobinemia have also been reported following exposure to hydrogen peroxide, and free methemoglobin may turn blood lines a brownish-blue hue on visual inspection.[76] A sudden onset of symptoms in multiple patients should trigger an immediate cessation of dialysis. Blood should not be rinsed back due to the risk of hemolyzed hyperkalemic blood being returned to the patient. A thorough investigation of the water system, dialysate, and machine should be undertaken.

Dialysis-Associated Thrombocytopenia

Dialysis-associated thrombocytopenia (DAT) was originally described as similar to dialysis-associated leukopenia—a transient complement-mediated process that returns to baseline by treatment end.[77] Thrombopoietin levels notably rise during the course of a dialysis session, perhaps due to subclinical treatment-related platelet loss.[78] A more concerning development than traditional DAT is heparin exposure and subsequent development of HIT. HIT may occur after exposure to either UFH or LMWH but is more common in the former.[79] Pathophysiology is thought to be the development of antibodies to PF-4. Typical appearance is 5–10 days after drug exposure (although this is variable), and HIT may present as access or recurrent filter clotting. HIT has been documented from various types of exposures, including heparinized saline, heparin catheter locks, as well as usual procedural anticoagulation.[80] Diagnosis is by clinical and laboratory criteria, and the American Society of Hematology (ASH) endorses the clinical "4 T's" scoring system while laboratory evaluation is pending.[81] Management is generally in conjunction with a hematologist, but general principles involve cessation of all exposures to heparin and using alternative anticoagulation agents. The direct thrombin inhibitors argatroban and bivalirudin have been successfully used in dialysis procedure anticoagulation. There is also a case report of apixaban usage to treat HIT in the setting of acute kidney injury requiring dialysis; however, direct oral anticoagulants are not currently recommended by ASH guidelines.[82]

Pulmonary Complications

Given the high prevalence of structural heart disease, intrinsic lung disease, and sleep apnea in patients with ESKD, there are myriad potential causes of hypoxia and hypercarbia.[63] Traditional dialysis-associated hypoxemia has been described for decades. The pathophysiology is unclear. Originally, leukocyte sequestration in the pulmonary vasculature (described earlier) was thought causative, although this has been disputed. The prevalence of prolonged hypoxemia during dialysis was estimated at 10% in one study of nearly 1000 prevalent in-facility dialysis patients.[83] Hypoxemic patients were noted to have higher rates of hospitalization and mortality during long-term follow-up. Etiologies such as dialyzer material, buffer material (high bicarbonate baths) leading to alkalosis, and anemia have also been suggested.[84] Treatment is generally supportive, and investigation of non–treatment-related causes should be undertaken and corrected where possible.

Technical Issues

Technical complications of the procedure resulting in patient harm are rare but can be fatal. Here, we will briefly review air embolism and dialysate composition errors.

Air Embolism

Air embolism is a dreaded complication of dialysis. Given the complexity of the dialysis procedure, there are a number of ways air can enter: equipment failure, disconnected or cracked catheter, or cracks in dialysis tubing. Without air alarms and air traps to capture inadvertently introduced air, the high pressures generated by the blood pump would rapidly deliver gas into the dialysis access. The pathophysiology of air embolism varies depending on cardiovascular anatomy. For most, air is sent to the right atrium and ventricle where even small volumes—0.5 mL/kg in animal studies—can cause death by lodging in the pulmonary circulation. Patients with a patent foramen ovale or intracardiac shunt are at risk of paradoxical emboli crossing into the arterial circulation, which can lead to cerebral emboli, particularly if upright. Symptoms are classically described as chest pain, shortness of breath, and a sense of "impending doom." Treatment is supportive in the facility and involves placing the patient in the left lateral decubitus position with head down—Durant's maneuver to attempt to trap air in the right atrium and ventricle. Supplemental oxygen should also be administered.

Dialysate Composition

Dialysate is typically generated from medical-grade water, acid concentrate containing electrolytes, and a buffer (base) that may be liquid or powder. The precise mixing of these elements is handled by proportioning systems. The composition of the dialysate is checked by electrical conductivity meters within the machine. Dialysate can be generated centrally and disbursed or locally at the machine itself. Patient harm may occur when the proportioning systems improperly mix dialysate and safety features of the dialysis machines, such as the conductivity meters, fail. Examples include seizures induced by acute hypernatremia from excessive bicarbonate and hypotonic dialysate, causing massive hemolysis.[85,86]

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12

Hemofiltration and Hemodiafiltration

MARTIN K. KUHLMANN, MD

Introduction

Conventional hemodialysis (HD) is based on diffusive transport of solutes across a semipermeable membrane and is effective in removing water-soluble small-molecular-weight (MW) solutes and electrolytes. The removal of solutes with larger molecular sizes, such as phosphate and β_2-microglobulin, however, is limited by diffusive resistance. Because insufficient removal of these larger uremic toxins may contribute to the high cardiovascular mortality risk observed in these patients, the need for better removal of those solutes has become evident. It has long been known that larger molecules can be removed across membranes more efficiently by convective transport, which is less size limited than diffusive clearance.

In the 1970s, hemofiltration (HF) was developed as a pure convective therapy, which was later followed by the introduction of hemodiafiltration (HDF), which combines the advantages of diffusion and convection into one therapy. In both HF and HDF, plasma water is filtered across the dialyzer membrane in excess of the ultrafiltration volume (UFV) required to control hydration status. The volume of excessively filtered fluid is replaced into the blood in form of sterile, nonpyrogenic substitution fluid to maintain hemodynamic stability.

Initially, sterile replacement fluid was provided in plastic bags, and for reasons of cost and practicability, the total fluid replacement volume per session was therefore limited. The understanding that sufficient removal of uremic middle-MW substances may be achieved by enhanced convective transport led to the development of on-line production of sterile, nonpyrogenic replacement fluid. With modern on-line HDF (ol-HDF) machines, nearly unlimited volumes of dialysate and substitution fluid can be produced, and therefore, much higher convection and substitution volumes are achieved. Among all intermittent extracorporeal treatment strategies, ol-HDF has the potential to provide the largest removal of the widest range of solutes.

Currently, ol-HDF is used in routine clinical practice for more than 10% of the European dialysis population, with an increasing trend. In northern European countries, more than a quarter of patients and in Switzerland, more than 60% of dialysis patients are treated with ol-HDF. In the United States, ol-HDF was only recently approved by the Food and Drug Administration but is currently used only rarely.

Definitions

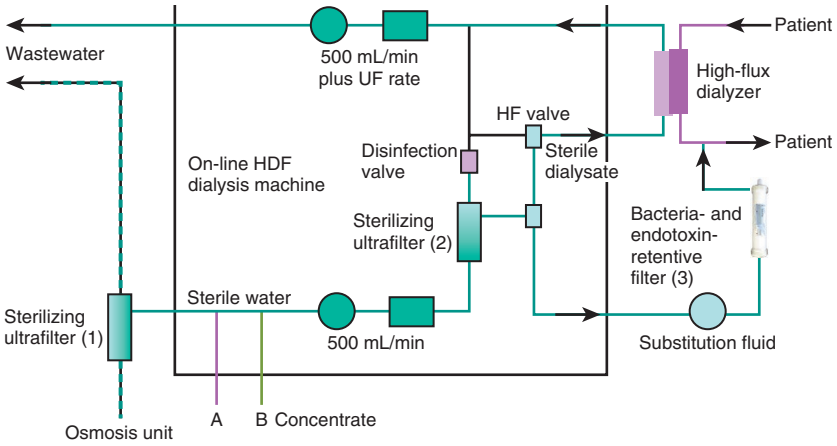
In *hemofiltration*, water, and solutes from the blood compartment are driven by positive hydrostatic pressure across a semipermeable membrane into the filtrate compartment, from where it is drained. With the flow of water, small and large solutes get dragged through the membrane at a similar rate (solvent drag effect). Dialysate is not used in HF.

Hemodiafiltration is defined by the European Dialysis (EUDIAL) working group as extracorporeal blood clearance treatment that combines diffusive and convective transport using a high-flux dialyzer with ultrafiltration (UF) coefficient > 20 mL/mm Hg/h/m^2, a sieving coefficient for ß2-microglobulin > 0.6, and a percentage of effective convective transport > 20% of the total processed blood.

Convection volume (*CV*) is defined as the achieved total UFV, the sum of the replacement volume, and the intradialystic weight loss obtained over an entire HDF session.

Preparation of Ultrapure Replacement Fluid: Technical Issues

Water used for convection-based therapies needs to fulfill very stringent criteria of chemical and microbial purity, which has led to the concept of "ultrapure water," which means virtually sterile and nonpyrogenic. The basic technical setup includes pretreatment of regular community drinking water by microfiltration, activated charcoal, and downstream microfiltration, followed by two reverse-osmosis modules in series. Such ultrapurified water is delivered to dialysis machines, and ultrapure dialysate is produced by "cold sterilization" of freshly prepared regular dialysis solution using additional sterilizing ultrafilters. Finally, replacement fluid is generated online by filtering ultrapure dialysate through bacteria- and endotoxin-retentive filters to prepare a sterile and nonpyrogenic solution that can be immediately infused into the patient (Fig. 12.1).



• **Fig. 12.1** Hemodiafiltration (*HDF*) dialysis and substitution fluid circuit. Ultrapurified water is delivered from the osmosis unit and is sterile filtered through sterilizing ultrafilter *(1)*. Freshly prepared regular dialysis solution is then "cold sterilized" using the additional sterilizing ultrafilter *(2)*, thus generating ultrapure dialysate. "Sterile" replacement fluid is generated online by filtering ultrapure dialysis fluid through a bacteria- and endotoxin-retentive filter *(3)* to prepare a sterile and nonpyrogenic solution, which in postdilution HDF is infused to the patient downstream to the dialyzer. *HF*, Hemofiltration; *UF*, ultrafiltration.

Modes of Hemodiafiltration

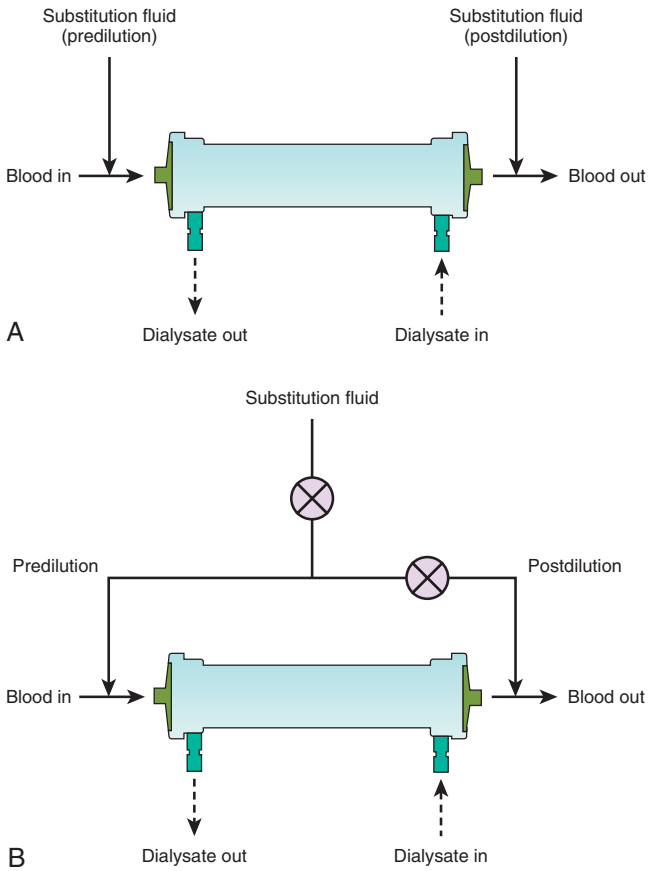
Modes of HDF are defined by the site in relation to the dialyzer, where replacement fluid is infused into the patient's blood.

Postdilution Hemodiafiltration

This is the most common form of ol-HDF worldwide and the HDF mode best studied in randomized controlled trials (RCTs). In the postdilution mode, replacement fluid is infused downstream of the dialyzer, usually into the venous bubble trap (Fig. 12.2A). The concentration of filtered substances in the ultrafiltrate depends on the sieving coefficient for each compound. For solutes with a sieving coefficient of 1, which can pass the membrane unimpeded, the concentration in the ultrafiltrate will be identical to the plasma water concentration. Because UF is enforced on undiluted blood, hemoconcentration occurs within the blood compartment of the dialyzer. Postdilution HDF is the most efficient mode in terms of increasing solute removal.

Predilution Hemodiafiltration

In the predilution mode, the replacement fluid is added upstream of the dialyzer, thereby diluting the patient's blood (see Fig. 12.2B). In contrast to the postdilution mode, filtration rates up to 100% of blood flow rate are possible. However, predilution reduces the efficiency of both the diffusive and convective components by reducing the solute blood concentration and, thus, the solute gradient. For equivalent clearance, the ultrafiltration rate (UFR) in predilution mode needs to be about two times that of postdilution HDF.



• **Fig. 12.2** Hemodiafiltration modes. **A,** In the predilution mode, the substitution fluid is infused upstream; in postdilution mode, it is infused downstream of the dialyzer. **B,** In the mixed-dilution mode, the substitution fluid is infused upstream as well as downstream of the dialyzer. In the mixed-dilution mode, the relation of predilution to postdilution volume depends on various factors affecting blood side hemoconcentration.

Mixed-Dilution Hemodiafiltration

In the mixed-dilution mode, the replacement fluid is infused both upstream as well as downstream of the dialyzer. The ratio of upstream and downstream infusion rates can be varied to achieve the optimal compromise between maximizing clearance and avoiding the consequences of high transmembrane pressure and hemoconcentration.

Mid-Dilution Hemodiafiltration

Here, the replacement fluid is infused within specifically designed dialyzers partway down the blood pathway. Thus, the first part of the blood circuit is operated in postdilution mode, and the second part, in predilution mode.

Enhanced Internal Filtration/Backfiltration, Expanded Hemodialysis

The term "expanded HD" (HDx) is used for a treatment where diffusion and convection are enhanced to a level comparable with HDF but without the need for replacement fluid using hollow-fiber dialyzers specifically designed for high rates of internal filtration and backfiltration equipped with high retention onset, medium cut-off (MCO) membranes. MCO membranes allow diffusive removal of larger middle molecules up to 45 kDA without significant albumin loss. A high convection flow is generated in the proximal part of the dialyzer by internal filtration, while backfiltration occurring in the distal part compensates for the excessive filtration rate. This process is regulated by the UF control system of standard dialysis machines, providing the exact amount of net filtration required for the scheduled weight loss without the need for reinfusion. Whether HDx produces a significant effect in dialysis outcomes still needs to be examined in clinical trials. Internal filtration/backfiltration is not considered a form of HDF by the Food and Drug Administration.

Clinical Advantages of On-Line-Hemodiafiltration

High-volume convective techniques may be associated with several clinical benefits. HDF may provide superior control of hyperphosphatemia and reduce cardiovascular risk, improve inflammatory status, and preserve lean tissue mass. It may also enhance hemodynamic stability and provide superior control of fluid overload, left ventricular hypertrophy, arterial endothelial function, and propensity for serum calcification. Neurological symptoms such as restless leg syndrome, polyneuropathy, and itching due to the accumulation of uremic toxins may disappear. Several RCTs and meta-analyses show that in HDF, blood pressure stability is superior compared to standard HD, and the incidence of symptomatic intradialytic hypotension is reduced. It is not clear whether this also translates into protection from myocardial stunning. Patient satisfaction and quality of life, including social, physical, and professional activities, have been reported enhanced in postdilution HDF compared to high-flux HD.

Ol-HDF appears to be beneficial for children on dialysis in terms of reversing uremic growth retardation and promoting catch-up growth. These effects may also be mediated by secondary factors related to the enhanced removal of middle-MW solutes, such as free diet, good appetite, reduced inflammation, less fatigue, and no metabolic acidosis, leading to less malnutrition and increased daily activity.

Effect on Survival

Several large prospective RCTs (Convective Transport Study (CONTRAST), Estudio de Supervivencia de Hemodiafiltración On-Line (ESHOL), Turkish HDF Study, French Convective versus Hemodialysis in Elderly (FRENCHIE)) have failed to demonstrate convincingly that survival with postdilution HDF is superior to survival with conventional low- or high-flux HD in prevalent patients. However, there were major differences in mean delivered HDF dose among the trials, and each of three trials with mortality as a primary outcome showed a dose–effect relationship between achieved effective CV and mortality. Those patients receiving the highest effective CV had a consistently significant lower mortality risk compared with control patients and patients receiving lower HDF doses.

Further, an individual participant data meta-analysis for all 2797 participants of the four RCTs indicated that all-cause and cardiovascular mortality were significantly reduced by ol-HDF 14% and 23%, respectively, and even stronger (22% vs. 31%, respectively) by *high-volume ol-HDF* when the average achieved CV exceeded 23 L/1.73 m^2. The survival advantage was not restricted to selected patient groups based on age, comorbidity, or dialysis vintage. Several recently published registry data support the survival advantage for ol-HDF.

Current data from meta-analyses, plus the fact that both generation rate as well as distribution volume for uremic toxins are related to body mass, make it reasonable to prescribe target CV in relation to a measure of body size, such as body surface area (BSA). Current recommendations suggest a target CV of 26 L/1.73 m^2 BSA (> 15 L/m^2 BSA) per session for three sessions per week. Whether these targets will improve hard outcome parameters is currently under study in the international comparison of high-dose hemodiafiltration with high-flux hemodialysis trail (CONVINCE).

Principles of the Hemodiafiltration Prescription

Quantifier of Hemodiafiltration Dose

Traditionally, dialysis dose is defined by mass removal of uremic toxins, with urea being used as a surrogate marker for the elimination of water-soluble small-MW toxins. Because urea clearance during HD barely increases when convection

is added, urea removal cannot be used as a marker of middle molecule clearance in HDF. For higher-MW solutes, mass removal during HDF is directly related to the *effective* CV, with the term "effective" relating to the *undiluted* total UFV, which is identical to total CV in postdilution mode.

Membrane Selection

To guarantee unimpeded filtration of fluid and higher-MW solutes throughout the treatment session, selection of an adequate dialysis membrane is essential. High-flux membranes offering both a high hydraulic permeability and a high middle-molecule clearance are required. Whereas hydraulic permeability is reflected by the membrane UF coefficient, membrane permeability is defined by the sieving coefficients (S) for selected middle molecules. For high-volume ol-HDF, a high-flux membrane with a UF coefficient > 0 mL/h/mm Hg/m^2 and a sieving coefficient for β_2-microglobulin greater than 0.6 are required.

Blood Flow Rate, Filtration Fraction, and Treatment Time

The two major aims governing the prescription of HDF dose are (1) adequate delivery of the target effective CV and (2) prevention of excess hemoconcentration. The major determinants for dosing prescription are blood flow rate (Qb), filtration fraction (FF), treatment time (TT), and HDF mode.

In *postdilution*, ol-HDF UF from undiluted blood leads to hemoconcentration and lowering of Qb within the dialyzer, promoting the deposition of plasma proteins on the membrane surface, clogging of membrane pores, and occlusion of blood channels. These effects can raise transmembrane pressure, cause safety alarms, reduce clearance, or result in filter clotting. Blood viscosity is also affected by hematocrit and concentration of blood proteins.

The **blood flow rate** needs to be optimized to minimize the effects of hemoconcentration. As explained later, Qb is directly related to TT required to achieve the target CV and should be individualized for each patient, taking into account vascular access characteristics and the potential presence of conditions that increase blood viscosity, such as high hematocrit, cryoglobulinemia, and gammopathies. Ideally, a Qb of 300 mL/min or higher is recommended, but a lower Qb does not preclude successful high-volume HDF. It is essential to measure recirculation when optimizing Qb repeatedly.

Filtration fraction describes the relationship between the UFR and Qb and is defined as the fraction of plasma water that is filtered during passage of blood through the dialyzer. To avoid excessive hemoconcentration, FF should be limited to 25% to 30% of Qb. Higher FF up to 30% can be safely executed only with modern dialysis machines designed to optimize UFR based on automated adjustment of transmembrane pressure.

Treatment time has to be recognized as an important prescription variable to achieve the effective target CV in high-volume HDF. Total TT required to reach the prescribed CV may be calculated from prescribed Qb, FF, and UFR:

$$\text{UFR} = \text{Prescribed bloodflow rate} \times \text{Prescribed FF} \quad (12.1)$$

$$\text{TT} = \text{Prescribed CV} / \text{UFR} \quad (12.2)$$

Complete and regular delivery of the prescribed target CV should become the priority in high-volume ol-HDF, with TT being an important variable in cases in which inadequate vascular access limits Qb. When achievement of target CV is given highest priority, then TT may vary from treatment to treatment depending on individual Qb and FF. A summary of prescription details for high volume ol-HDF is given in Table 12.1.

Selection of Hemodiafiltration Mode

CVs > 20 L per session may be difficult to achieve in postdilution mode when TT is fixed to a maximum of 4 hours. In these cases, pre- or mixed dilution modes may be applied. However, in these modes, the CV required to remove a given mass of solutes is significantly higher than in the postdilution mode because of the dilution of blood solutes by upstream infusion of the replacement fluid. In these cases, the target CV will be the effective CV (target CV in postdilution mode) multiplied by a dilution factor, which is 2.0 for predilution mode and approximately 1.3 for mixed-dilution mode.

So far, no larger RCTs have compared the various dilution modes and their effects on patient outcomes. In the future, mixed-dilution HDF with feedback control of transmembrane pressure may become the method of choice to achieve target CV in a reasonable TT.

Anticoagulation

Adequate anticoagulation is a prerequisite for successful high-volume ol-HDF treatment. It is important to realize that when infused upstream of the dialyzer, a relevant loss of anticoagulant may occur during the first pass through the dialyzer because of high removal rates for non-protein-bound LMW (≤ 80%) or unfractionated heparin (≤ 50%). Therefore, the initial heparin bolus should be infused via the venous needle or blood line and allowed to mix with patient blood for at least 3 to 5 minutes before initiating extracorporeal blood flow.

Indications for Hemodiafiltration

Solid indications for ol-HDF have not been defined and await the results of ongoing clinical trials. Since the possible beneficial clinical effects are consistent in different patient groups, including age, gender, dialysis vintage, diabetes, or the absence or presence of residual kidney function, high-volume ol-HDF may be considered in patients with

- recurrent intradialytic hemodynamic instability
- inadequate dialysis dose with conventional HD

TABLE 12.1 Prescription Details for High-Volume On-Line Hemodiafiltration

Parameter	Target Range
Hemodialyzer	
Membrane	High flux, 1.6–2.2 m^2
Fiber internal diameter	≥200 μm
Ultrafiltration coefficient	>20 mL/h per 1 mm Hg per 1 m^2
Sieving coefficient	>0.6 for β_2-microglobulin; <0.001 for albumin
Vascular Access	
AVF or AVG; tunneled central venous catheter	Needles, 14–15 G
Blood flow rate	350–450 mL/min
Dialysate Flow Rate	
Total (including substitution solution)	600–1000 mL/min
Dialyzer	500–600 mL/min
Convection Volume	
Postdilution	23 L per treatment or 26 L/1.73 m^2
Predilution	46 L per treatment or 52 L/1.73 m^2
Mid-dilution or mixed dilution	35 L per treatment or 40 L/1.73 m^2
Ultrafiltration Control	
Manual	TMP <400 mm Hg. Filtration fraction <0.25
Automated	TMP = 105–300 mm Hg
Anticoagulation	
Unfractionated heparin	No dose adjustment
Low-molecular-weight heparin	Dose and injection site adjustment
Dialysate composition	Adjusted according to patient need and convection volume

AVF, Arteriovenous fistula; *AVG*, arteriovenous graft; *TMP*, transmembrane pressure.
Derived from Canaud B, Vienken J, Ash S, Ward RA. Hemodiafiltration to address unmet medical needs of ESKD patients. *Clin J Am Soc Nephrol*. 2018;13:1435–1443.

- treatment-resistant hyperphosphatemia
- congestive heart failure
- severe cardiovascular complications
- calcific uremic arteriolopathy (calciphylaxis)
- Protein-energy wasting
- growth retardation (children)
- or as an elective therapy for incident patients before severe complications develop.

Safety of Hemodiafiltration

Because of the intravenous infusion of large volumes of replacement fluid, patients are exposed to additional risks related to the systems used to prepare the replacement fluid and control fluid balance. Therefore, HDF equipment needs to be subject to more stringent safety standards and regulatory oversight than equipment used for conventional HD.

In general, high-volume ol-HDF is considered a safe treatment modality. The various RCTs did not produce any signal that ol-HDF is an unsafe treatment modality and demonstrated that substitution fluid of adequate quality and quantity could be produced online over a prolonged period of time without increasing the risk for infection or inflammation. In fact, in some of these studies, mortality risk from infectious causes was even significantly lower in ol-HDF than in HD. Potential long-term risks of high-volume HDF are related to the occurrence of deficiency syndromes caused by increased removal of proteins, vitamins, nutrients, and other solutes. Supplementation of vitamins B_{12} and folate, trace elements such as zinc and selenium, and other micronutrients, as well as regular monitoring of vitamin C and serum albumin levels, is therefore recommended.

Summary—High-Volume On-Line Hemodiafiltration in Clinical Practice

High-volume ol-HDF may become the standard mode of treatment once superior survival versus conventional HD has been documented in the ongoing CONVINCE trial. Until then, high-volume ol-HDF may be viewed as an alternative treatment option for maximum diffusive and convective elimination of higher-MW solutes.

Recommended Reading

Blankestijn PJ, Grooteman MP, Nube MJ, Bots ML. Clinical evidence on haemodiafiltration. *Nephrol Dial Transplant.* 2018;33:iii53–iii58.

This review gives a brief overview of the presently available evidence of the effects of HDF on clinical end points, speculates on the possible mechanisms of a beneficial effect of HDF as compared with standard HD, and ends with some perspectives for the future.

Canaud B, Vienken J, Ash S, Ward RA. Hemodiafiltration to address unmet medical needs of ESKD patients. *Clin J Am Soc Nephrol.* 2018;13:1435–1443.

An excellent deep and detailed discussion of the current state-of-art in hemodiafiltration.

Ledebo I, Blankenstijn PJ. Haemodiafiltration—optimal efficiency and safety. *NDT Plus.* 2010;3:8–16.

A classic paper on the basics of diffusive and convective elimination, the different HDF modes, and safety standards of dialysis and replacement fluid preparation.

Locatelli F, Carfagna F, Del Vecchio L, La Milia V. Haemodialysis or haemodiafiltration: that is the question. *Nephrol Dial Transplant.* 2018;33(11):1896–1904.

Summary and discussion of nonconsistent clinical results reported in three recent RCTs on ol-HDF vs. conventional HD.

Maduell F. Hemodiafiltration versus conventional hemodialysis: should "conventional" be redefined? *Semin Dial.* 2018 Nov.;31(6):625–632.

The author opens the discussion about the redefinition of the term "conventional" treatment for ESRD patients. It is proposed that the time has come to consider HDF as the conventional hemodialysis treatment.

Peters SAE, Bots ML, Canaud B, et al. Haemodiafiltration and mortality in end-stage kidney disease patients: a pooled individual participant data analysis from four randomized controlled trials. *Nephrol Dial Transplant.* 2016;31:978–984.

Individual participant data meta-analysis of all patients recruited by four RCTs comparing HDF and high-flux or low-flux HD. This publication is the basis for ongoing clinical trials.

Piccoli GB, Nielsen L, Gendrot L, Fois A, Cataldo E, Cabiddu G. Prescribing hemodialysis or hemodiafiltration: when one size does not fit all—the proposal of a personalized approach based on comorbidity and nutritional status. *J Clin Med.* 2018;7:331–354.

A very relevant discussion of a personalized approach to HD and HDF prescription with particular attention placed on the vulnerable elderly high-comorbidity population.

Tattersall JE, Ward RA. Online haemodiafiltration: definition, dose quantification and safety revisited. *Nephrol Dial Transplant.* 2013;22:542–550.

Report of the European Dialysis (EUDIAL) Working Group of the ERA-EDTA on an international consensus conference on terminology, safety, and efficacy of ol-HDF.

Ward RA, Vienken J, Silverstein DM, Ash S, Canaud B. Regulatory considerations for hemodiafiltration in the United States. *Clin J Am Soc Nephrol.* 2018;13:1444–1449.

A review on the safety of on-line HDF with a focus on the online production of large volumes of substitution fluid infused directly into the bloodstream.

13

Wearable and Implantable Renal Replacement Therapy

WILLIAM HENRY FISSELL IV, MD

Introduction

Dialysis is the semi-selective removal of solutes from a solution by diffusion across a semipermeable membrane. It was first used in vitro by Thomas Graham in 1861 to separate ions from macromolecules in a colloidal solution. Early in the 20th century, John Jacob Abel isolated epinephrine, insulin, and other hormones from the blood of living dogs using dialysis, which he termed "vividiffusion." Kolff is generally credited with the first successful dialytic treatment of kidney failure in a human patient in 1944. Alwall independently developed a hard-shell dialyzer, allowing for pressure-driven ultrafiltration to control extracellular fluid volume in addition to solute clearance. In 1960, Scribner, Quinton, and Dillard developed a reliable make-and-break connection to the circulation, the Scribner shunt, and maintenance hemodialysis became possible. The technology and medical, economic, and social infrastructures of dialysis have evolved so that by 2020, over 500,000 American patients with end-stage kidney failure are able to survive for months and years after the diagnosis of kidney failure. Dialysis is thus the first engineered replacement for a failed vital organ and has been successful in that a procedure that 50 years ago was rationed due to scarcity is now the standard of care. Recent literature has suggested that overenthusiastic prescription of dialysis to inappropriate patients is a concern, rather than appropriate use of a scarce resource.

A patient dependent on hemodialysis is medically distinct from a patient with normal kidneys or advanced chronic kidney insufficiency. Some of the most compelling data in this regard are the vastly prolonged survival of kidney failure patients who receive a transplant compared to those remaining on the waitlist for an organ. Time to first appropriate shock from an implantable defibrillator is much sooner in dialysis patients than in those with chronic kidney disease, and epicardial atherosclerosis appears much more resistant to therapy in dialysis patients compared to subjects without kidney failure. Patients dependent on dialysis have impaired vaccine responses and die of pulmonary infection at a rate 20 times the rate in the general population. Young women with kidney failure on dialysis often do not menstruate and rarely conceive or carry a pregnancy to term. The clinical presentation of a dialysis patient who is "well dialyzed" by present standards may be disappointingly similar to the presentation of a patient with kidney failure who has not been dialyzed at all.

Limits of Conventional Hemodialysis

Maintenance hemodialysis is an episodic extracorporeal membrane blood purification procedure, and in the United States, it is generally performed three times each week for 3 to 5 hours a session. Dialysis dose is in practice adjusted by setting the duration of the treatment. Treatment time is chosen in order to clear approximately one volume of distribution of urea per patient per treatment, using a membrane that has an area approximately equivalent to the patient's body surface area. Urea is, in many ways, a sensible choice for a biomarker of dialytic adequacy, as the nitrogenous wastes of protein metabolism are clearly linked to acute uremia, and diets that are sparing in protein can delay the onset of uremic symptoms when dialysis is not feasible. This episodic treatment pattern is essentially unlike the continuous, around-the-clock solute removal of healthy kidneys. In this section, we describe how the episodic treatment schedule of dialysis contributes to the morbid phenotype of dialyzed kidney failure.

Solute Removal

Urea

Urea is the end product of protein metabolism. Typical dietary protein intake in adults results in about 10–13 mg/min of urea nitrogen production. In the course of a dialysis session, small solutes are removed in proportion to their concentration. In the case of urea, a two-compartment

first-order kinetic model describes urea removal well, and a single-compartment model is sufficient for most urea kinetic modeling.

$$C = C_{initial} e^{\frac{-Kt}{V}} \quad (13.1)$$

Where K is the instantaneous clearance, V is the volume of distribution of urea, and t is treatment time. A Kt/V of 1.0 is approximately equivalent to a dialysis session clearance of one urea volume of distribution. In practice, there is some urea rebound from the (not modeled) peripheral compartment, and so the targeted single-pool Kt/V target is 20%–40% higher than 1.0. From this, we can estimate net urea removal in a single session:

$$Urea\ Removal = C_i K \int_0^t e^{\frac{-Kt}{V}} dt \quad (13.2)$$

Over 2 days between dialysis sessions, somewhere between 28 and 43 g of urea will be generated and need to be removed. As removal is concentration dependent, one might ask, how high must the predialysis urea nitrogen rise to achieve this removal? Hemodialysis urea clearance is usually limited by blood flow rather than dialysate flow or membrane efficiency. If we assume K is around 300–350 mL/min, we can evaluate the integral in Eq. 13.2 and determine that the predialysis urea nitrogen must rise to around 70 mg/dL or greater to remove urea generated at a rate of 10 mg/min. The time-averaged urea concentration is likely close to 40 mg/dL. The lesson is that in maintenance dialysis on a thrice-weekly schedule, azotemia is the price of nutrition. The dialysis patient with a low predialysis blood urea nitrogen (BUN) either has significant residual renal function or is not eating enough protein.

In contrast, the time-averaged concentration of any solute that is continuously cleared by a first-order mechanism tends toward the ratio of the generation rate to the clearance (G/K). If urea is generated at 10 mg/min and cleared at 15 mL/min, the long-term concentration will be about 0.66 mg/mL or 66 mg/dL. If we double the clearance to 30 mL/min, the time-averaged concentration will still be elevated: 33 mg/dL.

Phosphorus

Phosphorus is an unusual molecule in dialysis. Inorganic phosphate is a small molecule with a molecular weight (100 Da) less than that of creatinine (113 Da); it is negatively charged and passes through modern dialyzer membranes slightly less freely than creatinine. However, dialytic removal of phosphorus is inadequate to balance dietary intake, so dietary restriction and oral phosphorus binders are required to keep phosphorus levels low. Very few dialysis patients are able to attain target phosphorus levels through dialysis, binders, and diet. The basis for limited dialytic removal of phosphorus is that phosphorus is best described by a multicompartment kinetic model with nonlinear kinetics. Extracellular phosphate falls rapidly during treatment, decreasing the concentration gradient that drives removal, but refilling the extracellular space from intracellular stores is slow. Thus, hemodialysis can extract phosphorus from blood but not from all body tissues. Interestingly, phosphorus concentrations in blood fall precipitously; but then plateau as incompletely understood regulatory mechanisms mobilize phosphorus from reservoirs, possibly bone, to prevent more severe hypophosphatemia. The role of intradialytic hypotension in decreasing blood flow to phosphorus-rich tissues, such as striated muscle remains uncertain, but it is a plausible factor complicating dialytic phosphorus removal. In contrast, continuous renal replacement therapies (CRRTs), as practiced in some critical care units, have instantaneous clearances an order of magnitude lower than hemodialysis but can remove so much phosphorus over 1 to 2 days that supplementation is often needed. This is not surprising as one recalls that long-term steady-state serum concentrations will tend towards G/K. To balance dietary absorption of 800 mg/day or 0.5–0.6 mg/min, an instantaneous clearance of only 15 mL/min can maintain phosphorus levels of about 3 mg/dL. More than that, as in CRRT, will always drop levels lower.

β_2-Microglobulin

A significant difference between glomerular filtration and hemodialysis is the clearance of so-called middle molecules between 2 and 25–40 kDa, although definitions vary. β_2-Microglobulin is an approximately 12-kDa protein member of the immunoglobulin superfamily of proteins. It is expressed on the surface of all nucleated cells as a component of type I major histocompatibility complex. β_2-Microglobulin passes through the glomerular capillary wall almost unimpeded. In contrast, β_2-microglobulin is not well cleared by conventional hemodialysis membranes. Even high-flux and high-cutoff dialyzers have β2-microglobulin clearances 10%–20% of the urea clearance. While β_2-microglobulin levels in serum may fall by half during a treatment, postdialytic rebound from peripheral compartments is considerable. β_2-Microglobulin is not merely a benign marker of middle molecule clearance but is mechanistically pathological in end-stage kidney disease. β_2-Microglobulin polymerizes to form amyloid, and over time, this affects nearly every organ system from nerve entrapment in the carpal tunnel to immune response to cardiovascular disease. So, in part, the barrier confronting dialytic management of β_2-microglobulin in the setting of thrice-weekly in-center dialysis is twofold: the dialyzer membranes do not allow much β2-microglobulin to pass through them, and β2-microglobulin is somewhat sequestered in a peripheral compartment.

The disappointing middle molecule clearance of hollow-fiber dialyzers is likely related to the underlying technology used to manufacture polymer membranes. While membranes are loosely described as having a "cutoff," even idealized membranes such as track-etch membranes or microfabricated membranes do not show an abrupt transition from unhindered passage to complete retention at some

particular solute size or weight. Instead, there is a transition range of molecular weights that are partially and incompletely retained. The pores in polymer membranes are formed using a solvent demixing process. A polymer is dissolved in a mix of incompletely miscible solvents. Typically, the polymer partitions more strongly into one solvent than the other. Some condition, such as temperature, is changed, and the solvents separate into individual phases, one with and one without the polymer. Micro- or nano-sized droplets of one solvent form the pores within the mix of the other solvent and polymer. These droplets have a dispersion of sizes: they are not all uniform in radius, and consequently, the membrane has a thermodynamic distribution of pore sizes, most small but many large. Fluid flow will disproportionately channel through the large pores as resistance to flow varies as the fourth power of the pore radius. If passage of a large solute, such as albumin, is to be blocked, there must be diminishingly few large pores. There are two ways to achieve this. First, the pore size distribution must be very narrow, with the droplets that form the pores being very uniform in size. Thus, there are few large pores. Second, the pore distribution must be based on a very small average pore size since the distribution will have tailed off so that there are few large pores. In practice, both paths are followed, but the mean pore size of most polymer dialyzers is much smaller than albumin and smaller even than the middle molecules we describe. For example, it is common to see myoglobin (a 15-kDa monomer) in urine, but even in cases of severe rhabdomyolysis, one rarely or never sees pigment in spent dialysate. We conclude that some of the difference between hemodialysis and native kidney function is not just the intermittent nature of hemodialysis but also due to the difference in pore size between the glomerulus and the dialyzer.

Protein-Bound Uremic Toxins

Microbial fermentation in the intestine generates an array of metabolites that varies from person to person and can change with diet. A number of fermentation products are small cyclic molecules that are highly protein bound. In the healthy kidney, these are not filtered by the glomerulus in any significant quantity as they are largely bound to plasma proteins, which are too large to pass through the glomerular filter. The relatively small free fraction of the solute in equilibrium with the bound fraction is filtered. However, they are renally excreted, and they accumulate in kidney failure. Many are thought to have causal roles in the residual syndrome of dialyzed kidney failure. Each renal tubule is surrounded by a capillary plexus of postglomerular blood. Organic anion and cation transporters on the basolateral surface of proximal tubule cells transport the free fraction out of the blood into the cytoplasm, and apical transporters excrete the solute into urine. In the peritubular capillaries, the continuous extraction of the free fraction gradually shifts mass balance so that more and more bound toxin equilibrates as unbound free toxins to be excreted. The same principle ought to hold in hemodialysis as well, except for two factors. First, the peritubular capillaries are working their gradual mass balance effect around the clock 168 hours per week, not just 12–15 hours during dialysis. The second factor is that the toxins are actively pumped out of the peritubular fluid, whereas in dialysis, a concentration gradient is needed to drive removal. Like urea, protein-bound uremic toxins (PBUTs) need to accumulate to high levels to drive removal. Several intriguing efforts are underway to alter the equilibrium binding of PBUTs during dialysis, including innocuous decoy toxins that bind to the site and displace the toxin, increasing the free fraction, and dialyzing against baths of varying temperature, ionic strength, and pH to increase the removal of PBUTs using conventional dialysis equipment.

Salt and Water Removal

The kidney, guided by redundant neuroendocrine feedback loops, maintains extracellular fluid volume to within a few kilograms despite widely varying salt and water intake. In the setting of chronic kidney disease, renal sodium handling gradually adapts to decreased glomerular filtration rates at the cost of a greatly narrowed range of sodium intake that can be managed. Patients who depend on hemodialysis gradually lose residual kidney function. Diuretic use can limit interdialytic weight gain and appears to delay loss of residual kidney function. Again, as in the discussion of urea earlier, the episodic nature of dialysis can explain some of the challenges in dialytic management of the end-stage kidney disease patient. Typical fluid intake in adults is around 1500 mL/day, and stool losses are usually only 100–200 mL/day. 1300 mL/day is a little over 9 L per week, although insensible losses may blunt that slightly. 9 L per week translates to 3 L of fluid removal per dialysis session. Patients who have diabetes or who do not carefully restrict their salt intake will experience osmolality-driven thirst and will drink more. Despite similar urea reductions, patients with interdialytic weight gains in excess of 3 kg had worse mortality than those with interdialytic weight gains less than 3 kg. Rapid removal of fluid during dialysis is associated with cardiovascular mortality. Acute decreases in intravascular volume, which occurs with ultrafiltration, can cause myocardial ischemia through several mechanisms. Dialysis patients with left ventricular hypertrophy, atrial fibrillation, or both will have an exaggerated hypotensive response to hypovolemia compared with healthy subjects. Catecholamine-mediated tachycardia in response to hypovolemia decreases the duration of diastole, and thus, the filling of epicardial coronary arteries. At the same time, systemic vascular resistance increases, increasing myocardial workload. Thus, demand ischemia is an understandable consequence of ultrafiltration, and echocardiography shows intradialytic myocardial stunning related to ultrafiltration. In contrast, prolonged or frequent dialysis sessions decrease intradialytic weight gain,

ultrafiltration rates, and decreased myocardial stunning, suggest that transient myocardial dysfunction is not intrinsic to the patient or the dialytic removal of solutes but instead directly related to the hemodynamic stresses of severe cyclic hypovolemia.

Wearable Systems

Very quickly after maintenance dialysis became feasible and reimbursed by Medicare in the United States, technology development for convenient dialysis emerged. It is worth considering that in the early 1970s, self-care hemodialysis at home was usual practice. The network of in-center dialysis facilities that provide the vast majority of hemodialysis in the United States had not yet emerged. Patients were essentially homebound during treatments. In the context of widespread self-care, the drive even then to facilitate portable, personalized systems is understandable. Kolff, Friedman, and others published theoretical and clinical data regarding portable and wearable systems in the 1970s. However, as in-center dialysis became more widely available, patients were relieved of the burden of bringing their equipment with them, as they could be reasonably assured of locating a facility that could accommodate them as they traveled. Dialysis accommodations for leisure travel became available as well. Thus, the need for portable or wearable systems for dialysis appeared less pressing, and efforts were directed elsewhere.

The episodic and intermittent nature of conventional dialysis poses barriers to health, and several groups have examined the role of intensive maintenance dialysis prescriptions with increases in treatment time, frequency, or both. The apparent benefits of these therapies and the growing recognition that less expensive and less burdensome treatment paradigms are possible have stimulated a resurgence in wearable or even implantable devices for the treatment of kidney failure. The most burdensome aspects of wearable systems for kidney replacement are broadly similar to key features of conventional dialysis. Vascular access, the Achilles heel of all dialysis procedures, is an especially thorny problem for wearable hemodialysis systems. The concept of conducting activities of daily living with one or more needles in a fistula or graft is anxiety-provoking. An accidental disconnect or venous needle dislodgement might not be immediately detected, and normal movement might allow the needle tip to traumatize the access. Catheter use is associated with inferior survival compared with a fistula or graft. It may be that patients who dialyze through catheters are substantially different from patients with fistulas and grafts, in vascular health, wound healing, and access to care. Requiring catheter access as a precondition for wearable hemodialysis may create a therapeutic quandary for physicians counseling patients regarding modality choice.

If we somewhat arbitrarily consider a minimum delivered dialysis dose equal to 10 mL/min, a device needs to supply at least 14 L of dialysate per day and, in general, much more. Typical dialysate requirements for conventional hemodialysis are on the order of 200 L; hybrid therapies such as NxStage, where dialysate flow need not be in great excess of blood flow may require 40–50 L per session. Peritoneal dialysis, which is the original "wearable" dialysis system, typically requires 10–15 L of dialysate. All of these volumes and their attendant weights are prohibitively cumbersome for a true wearable or implantable system. The cumbersome requirements for tens to hundreds of pounds of dialysate water have been recognized for decades. A longstanding and remarkably successful strategy to minimize water requirements has been the use of sorbents to regenerate fresh dialysate from waste dialysate.

The most widely used dialysate regeneration paradigm is clever and worthy of description. Spent dialysate bearing urea, potassium, phosphorus, and other organic uremic solutes are regenerated in a four-step process corresponding to each of these solutes. Dialysate is passed over a column bearing an enzyme, urease, that cleaves urea into ammonia and carbon dioxide gas. The pKa of the ammonia-ammonium (NH_3/NH_4^+) system is around 9, so the newly generated ammonia rapidly binds all free protons in the dialysate, raising the pH of the spent dialysate. The spent dialysate then passes through a cation exchange resin that absorbs NH_4^+, potassium, and other cations. Next, an anion-exchange column absorbs phosphate, sulfate, and other anions. Finally, a layer of activated charcoal absorbs creatinine and other organic solutes, as well as serves as a safety layer should the cation-exchange column become saturated and ammonia break through. The regenerated dialysate generally requires supplementation with calcium and magnesium to replace cations that bind to the cation exchange column, as well as supplementation with bicarbonate. Nevertheless, this approach was highly effective when implemented as the REDY system.

There are three commercial efforts at wearable systems for dialysis as of the date of writing. Public information about the state of development of technologies remains somewhat limited, which is understandable as entities protect trade secrets and corporate strategy, as well as navigate the regulatory environments in their potential markets. The descriptions of these technologies are based on published literature as well as personal communication with the medical end engineering leaders of each effort.

Peritoneal Dialysis

Peritoneal dialysis was the first form of "wearable" dialysis. Despite the much smaller dialysate volumes involved in peritoneal dialysis compared to hemodialysis, patients on peritoneal dialysis have enviable survival statistics and autonomy in fitting their treatment to their lives, and not the reverse. Recycling peritoneal dialysis with the REDY system was reported as early as 1976. AWAK Technologies in Singapore is developing a peritoneal dialysis-based automated wearable artificial kidney (AWAK) for around-the-clock therapy.

The device is described as being about the size of a paperback book, weighing 2 lb, and consisting of a small control module containing a pump and the electronics, an infusion reservoir containing electrolyte concentrates, and a larger disposable container of sorbents. The sorbent system appears to be very similar to the REDY system, using urease, zirconium oxide, and zirconium phosphate in tandem with activated carbon.

As with the REDY system, an infusion of divalent cations is essential to replace calcium and magnesium bound to the ion exchange column. Unlike the REDY system, peritoneal dialysis systems rely on an osmotic gradient between blood and dialysate to shift salt and water from the vasculature to the dialysate to be discarded. The standard osmotic agent in peritoneal dialysate is glucose, which is absorbed by the patient to varying degrees depending on the characteristics of the peritoneal membrane. As a result, the AWAK system infuses glucose, calcium, and magnesium. The key innovation of the AWAK device is its combination of *tidal peritoneal dialysis* with sorbents. In tidal peritoneal dialysis, small volumes and short dwells are substituted for large volumes and long dwells. The AWAK device has a total fluid volume of 750 mL divided into a tidal volume of 250 mL and a reserve volume of 500 mL. The 250 mL tidal volume is exchanged almost continuously to attain a flow rate of 4 L/h. In simulations with a commercial PD cycler operating in tidal mode, creatinine clearances of 10–11 mL/min, phosphate clearances of around 6 mL/min, and β_2-microglobulin clearances just under 2 mL/min were observed in human subjects. Whether the use of tidal peritoneal dialysis results in greater clearance is unclear; the technique may be selected for patient comfort and practical issues with catheter drainage. For the AWAK device, the primary benefit of a tidal prescription seems to be that less fluid, and thus, less weight is required. The ability of a recycling system to match the clearance of a conventional single-pass system is strongly dependent on avoiding saturation of the sorbents. In particular, if there is breakthrough of the cation exchange layer, ammonia generated by the urease layer could be transported to the patient with potentially devastating consequences. If the AWAK can deliver 10 mL/min creatinine clearance around the clock in a small portable package, this would be remarkable.

Results of a pilot human clinical trial of the AWAK system were presented in abstract form at the ASN Kidney Week in November, 2019. The study was small: 15 subjects were enrolled; 14 subjects completed at least one treatment. No efficacy data were presented other than pre–post solute levels. Adverse events included abdominal pain, bloating, and fibrin sheaths around the catheter. The company reports that a pivotal trial will begin enrolling in 2020.

Hemodialysis

There are two systems, both sorbent based, being developed for continuous ambulatory hemodialysis. The Wearable Artificial Kidney, or WAK, is presently in United States–based clinical trials following pilot studies in Vincenza, Italy. The large package size and high blood flow rates of conventional hemodialysis are not intrinsic to extracorporeal therapy. However, they are instead a consequence of the short treatment times used in conventional dialysis. Continuous therapy does not require dialyzer urea mass transfer coefficients in the thousands in order to remove urea and creatinine at high enough rates to balance endogenous production. Gura and colleagues combined a small rocker pump that alternately propels blood and dialysate through a small off-the shelf dialyzer. The dialysate is sequentially recirculated through a series of reactors containing the components of the REDY system. Syringe pumps supply calcium, magnesium, and heparin for anticoagulation. The apparatus can be worn similar to a utility belt, with a package weight of about 5 kg. Extensive effort was devoted to optimizing the efficiency of the reactors as improved efficiency results in decreased package size and weight.

Three clinical studies have been published describing the use of this technology. The combination of the pump system with a central venous catheter was first tested as an isolated ultrafiltration device in patients with symptomatic volume overload in the context of end-stage kidney disease. In 2006, six patients were treated for an average of 5.7 hours with no obvious adverse reaction, other than one patient experiencing a thrombosis of the central venous catheter. Mean ultrafiltration volume was slightly over 1 L. In 2007, Davenport and colleagues tested the WAK in eight patients with end-stage kidney disease. At a relatively modest blood flow rate (around 50 mL/min), they attained a urea clearance of 22 mL/min. The maxim that access, the Achilles heel of dialysis, was reaffirmed in that two vascular accesses clotted and one venous needle dislodgement occurred in eight treatment sessions. A follow-up study reported phosphate and β2-microglobulin clearances in the eight patients. Phosphate clearance was similar to urea clearance (21.7 mL/min), and β_2-microglobulin clearance was 11.3 mL/min. These data reinforce the previous comments: the rate-limiting step in solute removal may not be the dialyzer but rather intercompartmental clearances within the patient. Himmelfarb published the results of a pilot study at the University of Washington. The study intended to enroll 10 subjects but was halted after the seventh subject due to technical issues with the device. Five subjects completed 24 hours of treatment, and no adverse events were reported.

A different approach is adopted by a Netherlands-based company, Nanodialysis. Their sorbent-based approach has two fundamental differences from the REDY system and similar urease-zirconium-carbon regeneration schemes. First, the Nanodialysis system employs a FeOOH anion exchanger and a sodium polystyrene sulfonate cation resin with the intent that the resin is regenerated by the user. The principle is similar to the home water softener that removes minerals from well water. The solution of interest, such as spent dialysate, is circulated through the column. The cations and anions (e.g., potassium and phosphate) to

be removed from the solution displace the cations and anions on the column due to their higher affinity. When the column becomes saturated, it is switched out of the circuit and is bathed in a regeneration solution where bound cations and anions are driven off and washed away. In a dialysis device for home use, the total volume of electrolyte solutions could be decreased significantly, and the disposables cost of daily or twice-daily replacement of saturated sorbent cartridges is reduced as well.

The second innovation of Nanodialysis is that they dispense with the immobilized urease enzyme and instead employ an electrical current to oxidize urea to gaseous nitrogen, gaseous hydrogen, and carbon dioxide. This approach trades one set of challenges for another: the system does not have to manage ammonia generated by urease but will need to address gas generation by the recirculating system. The gas that is generated is removed from the dialysate by a degasser. The electrodes themselves are graphite based, avoiding possible leaching of heavy metals into the dialysate. Two papers describe the extracorporeal use of the system in healthy goats with few adverse events. The system's emphasis on urea removal and description of the activated carbon sorbent as effective for chlorine removal leaves removal of organic uremic toxins, such as p-cresol, kynurenic acid, or endogenous cardiac glycosides or drug removal, unanswered.

Fully Implantable Systems

A fully implantable device for treatment of kidney failure is the holy grail of tissue engineering. The Achilles heels of dialysis are access and infections, and a permanent internal connection to the vasculature could ameliorate both problems. There are challenges to the design engineering of implantable therapy. Present hollow-fiber dialyzers require superphysiologic pressures to circulate blood and have very limited-service lifetimes before fouling, and thrombosis reduces membrane clearances. Therapeutic strategies that involve replacement of saturated sorbent cartridges or supply of dialysate will continue to require periodic or chronic percutaneous access, with the risk of infection that repeated cannulation or a chronic catheter entails. Successful long-term implanted solutions for ESKD care will likely be based on strategies that avoid the need for dialysate or sorbents.

Recellularization Approaches

Several investigators have examined whether stem cells, engineered cells, or kidney-derived cells can be manipulated to rejuvenate an injured kidney or establish functioning nephrons within an engineered construct. Here, we discuss two approaches that have received widespread attention in the popular press, somatic cell nuclear transfer and "reanimation" of decellularized organs. We consider these together because they appear to share common challenges that threaten to delay clinical success for some time. Lanza and colleagues describe a strategy for cloning syngeneic donor tissue. Bovine oocyte nuclei were replaced with nuclei from allogeneic fibroblasts from a donor cow. These cloned oocytes underwent implantation and embryogenesis in a surrogate mother cow. Fetal calves were harvested at 5–6 weeks' gestation, and cells from specific embryonic organs were cultured and then implanted into the individual animal from whom the fibroblast nuclei had been originally isolated. Tissues from noncloned embryos were rejected by the host, while tissues from cloned embryos were not rejected by the syngeneic host. A small device made from hollow fibers, a collection pouch, and a cluster of embryonic kidney tissue formed clear fluid and was implanted in the animal's flanks. At explant, tissue that had histologic features of renal cortex was identified, and a small amount of straw-colored fluid was present in the collection pouch. The authors argued, on the basis of slightly elevated urea and creatinine levels as well as low glucose levels, that the cloned tissue had produced urine. However, the authors did not report albumin or protein concentrations in the fluid, which might have been a more convincing demonstration that their cloned tissue had formed functional nephrons.

The kidney has a highly elaborate spatial organization of blood vessels and epithelial cells that is essential to healthy function. This intricacy is challenging to design into an artificial construct. Investigators considered using the existing structures in an animal kidney as the scaffold onto which human kidney cells might be grown. Building on early successes with heart tissue, Ott and colleagues published an early result with rodent tissue in 2013. A decellularized rat kidney was seeded with human umbilical vein endothelial cells via the renal artery and a slurry of neonatal rat kidney cells via retrograde infusion into the ureter. After perfusion culture, the recellularized kidney was fixed, sectioned, and stained. Structures similar to glomeruli and tubules were identified. In vitro testing of recellularized implants showed creatinine clearances much less than matched cadaveric kidneys. Albumin retention was poor (47%), and glucosuria persisted, suggesting that differentiated function of engrafted cells was incomplete.

Both approaches are highly exciting as they are innovative strategies to expand the limited donor pool with organs for transplant. However, both approaches, as published, require the destruction of a fetus to obtain cells, which is ethically challenging for human applications. Both approaches rely, to some extent, on the idea that parenchymal cells retain their full differentiated identities despite extensive laboratory manipulation. If allowed to attach to a particular ecological niche consisting of extracellular matrix epitopes, paracrine signals from surrounding cells, and endocrine signals from the host, it is expected that the parenchymal cells will assume a phenotype with quantitative fidelity to some cell in a natural organ. Data supporting this idea are scarce; indeed, cell culture stress is common in vitro. Kidney podocytes, the glomerular cell most closely associated with filtration, have a fragile phenotype in vivo and do not assume the same phenotype in cell culture as they do in vivo. Growing replacement kidneys from isolated cells are likely to prove more complex than initially hoped.

Implantable Renal Assist Device

Fissell and Roy have pursued a biomimetic hybrid approach to build an implantable renal assist device (iRAD) as a permanent solution to end-stage kidney disease. Healthy kidneys are composed of a million or more nephrons. Each nephron is composed of two modules in tandem. First, a glomerulus that separates water and small molecules from the protein and cellular constituents of blood at a high enough rate to deplete the blood of wastes and toxins. In aggregate, the nephrons in a healthy adult kidney filter about 140 L/day of saltwater and toxins from the blood. Second, a long glandular structure lined with metabolically active epithelial cells reabsorbs 99% of the salt, water, glucose, and amino acids produced by the filter, progressively concentrating the filtered wastes into the 1–2 L of liquid urine we excrete every day. The renal assist device (RAD) is a large-scale extracorporeal bioartificial kidney that recapitulates the tandem filtration-reabsorption architecture of the kidney. The Kidney Project is a multidisciplinary effort to miniaturize the large-scale RAD to a compact and durable package for implantation: the iRAD.

Implantable Filters

Conventional dialyzer membranes are bulky, have short service lives, and are unsuitable for implantation. The idea of using kidney cells to grow glomeruli in the lab is an attractive alternative to artificial membranes. As of this writing, the cells that make up the kidney's filters appear to be terminally differentiated with limited regenerative potential and fragile phenotype. The specific cues needed to coax these cells into functioning filters remain unknown. A tissue-cultured glomerulus remains in the far future, so the iRAD requires an alternative to conventional polymer membranes and tissue-engineered filters. Roy and Fissell pioneered an entirely new membrane for kidney replacement. A new technology, silicon micromachining, allows precise control of pore size and shape. Roy developed thin-film membranes that copy the highly regimented and orderly structures of the glomerular slit diaphragm of the kidney. These silicon nanopore membranes optimize the permeability–selectivity tradeoff inherent to all membrane separation processes. Although silicon has been seen as a challenging biomaterial, especially for blood-contacting devices, highly hydrated polymer films effectively block the protein adsorption that initiates the coagulation cascade. Silicon membranes show promise in preclinical implant studies.

Bioreactor

The renal tubule has a remarkable ability to discriminate between metabolically valuable substrates and toxic wastes. The molecular mediators of uremia remain incompletely defined. In clinical practice, patients with prerenal azotemia may have extreme perturbations of urea and creatinine yet be cognitively intact, yet patients with tubular injury may have overt uremia despite less impressive laboratory measurements. The uncertainty regarding the mediators of uremia is a barrier to the design of passive devices. Humes pioneered the harvest, isolation, expansion, and packaging of kidney tubule cells into a therapeutic device. The choice of scaffold in the large-scale RAD, a hollow-fiber dialyzer, is a good one because, in addition to mechanical support, the dialyzer membrane is a barrier between the patient and the cultured cells. The molecular and cellular effectors of the innate and acquired immune response could not engage the allogeneic tubule cells, thus obviating the need for immune suppression. Thus, the best membrane for a hemofilter may also be repurposed as an excellent scaffold for the tubule cell bioreactor. The innovative silicon nanopore membranes that form the hemofilter of the iRAD also serve as a substrate for tubule cell growth.

Cultured renal tubule cells display metabolic features of the healthy tubule and respond to fluid shear stress in vitro.

Summary

A patient facing impending kidney failure has a wide variety of modality choices today: in-center conventional hemodialysis, in-center nocturnal dialysis, self-care home conventional, short daily, and nocturnal dialysis, or peritoneal dialysis. In the near future, the range of treatment possibilities will expand further to encompass a variety of wearable and implanted therapies. Each of the technologies discussed here would lower barriers to self-care of kidney failure and relocate ESKD care away from the dialysis facility. If these options emerge into the market, they could significantly reduce the cost of the $32B Medicare ESRD program. In FY2015, the National Institute of Health's budget allocation for the Division of Kidney, Urologic, and Hematologic diseases was $419.8 million: less than 2% of the annual cost of the Medicare ESKD program. All of us who care for patients with kidney disease hope that federal support for research on treatment of ESKD will come to match the immense burden of suffering and immense financial cost of dialysis.

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14

Home Preparation and Installation for Home Hemodialysis

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Introduction

Home hemodialysis has been available as a modality of kidney replacement therapy since the 1960s. The interest in home hemodialysis has been increasing over the past years because of its flexibility and benefits (which will be further discussed in the following section). Historically, home hemodialysis accounted for about 40% of the dialysis population in the United States in the 1970s and decreased in popularity in the 1980–90s. It is currently experiencing a resurgence in several countries, especially with the interest in more frequent or intensive hemodialysis. The U.S. Renal Data System (USRDS) 2019 Annual Data Report indicates that 62.7% of all prevalent dialysis patients were receiving in-center hemodialysis. Among the prevalent patients treated with hemodialysis, 2.0% used home hemodialysis.

Basis for Home Hemodialysis

Home hemodialysis offers several potential benefits as compared to conventional facility-based hemodialysis. These include better patient outcomes, increased freedom of time, cost reduction, as well as an improved quality of life.[1] Improvements in patient outcomes with more frequent or intensive home hemodialysis include better survival,[2] blood pressure control,[3] left ventricular geometry,[4] phosphate control and mineral metabolism,[5] quality of sleep,[6] and fertility.[7] Home hemodialysis offers more control from a patient's perspective over dialysis treatment scheduling and may afford greater flexibility in terms of employment. As compared to facility-based hemodialysis, home hemodialysis is cost-effective or cost-saving due to lower staff costs and likely medication costs. It may have better health outcomes in kidney disease–related quality of life and survival.[8,9]

Requirements

There are several prerequisites that need to be addressed before commencing a home hemodialysis program. A home visit should be conducted prior to further discussion of home dialysis to determine its feasibility and assess the necessary modifications. The availability of a checklist for the home visit may facilitate the process (Table 14.1).

There are multiple domains of requirements, including the following.

Legal

The local legal requirements regarding water supply, as well as land and housing, should be established to ascertain if home hemodialysis is feasible. There should be no legal restriction to the use of the building for the purpose of home hemodialysis. In addition, legal requirements concerning waste disposal, sewage, and electrical supply should also be established before the consideration of home hemodialysis. Consideration should be given toward specific policies regarding potentially biohazardous waste.

A unit policy should ideally be in place to decide who is financially responsible for the needed modifications to the home that may be necessary for plumbing and/or electrical renovations.

Water Preparation, Standards, and Plumbing

Home hemodialysis, as compared to conventional in-center hemodialysis, is potentially a more water-intensive procedure, with larger volumes of water being necessary to reconstitute the dialysate (except for the mobile platform). The total dialysate volume can range between 110 and 150 L for a 6- to 8-hour session of dialysis, as compared to 120 L for a typical conventional session. This makes water preparation and quality measurement critically important.

The water supply can come from various sources, for example, municipal water and feed water. Various water quality standards exist depending on where the dialysis is performed (International Organization for Standardization [ISO], Association for Advancement of Medical Instrumentation [AAMI]; Table 14.2), and the prevailing standards should

TABLE 14.1 Home Hemodialysis Initial Home Assessment Record

Checklist (to circle appropriately)				
Plumbing				
Water source	Well	City	Others	
Water conductivity				
Total chlorine				
Type of piping material used in plumbing				
Water pressure (psi) in home				
Source of water to RO	Wash room	Basement	Others	
Type of drain pipe	ABS	Copper	Cast iron	Others
Drainage to city or septic system	Flow open		Flow closed	
Can system above handle RO and machine reject water	Yes		No	
Electrical				
Space available on breaker panel	Yes		No	
Type of panel (name)				
Storage space				
Appropriate area selected for storage	Yes		No	
Area free of pest infestation	Yes		No	
Dampness/water damage present	Yes		No	
Room for stock rotation	Yes		No	
Adequate space for dialysis room	Yes		No	

ABS, acrylonitrile-butadiene-styrene; *RO*, reverse osmosis.

TABLE 14.2 Water Quality Standards for Dialysis Water*

Microbiologic Level		
	AAMI	**ISO**
Dialysis Water		
Colony-forming units (CFU)	< 100 CFU/mL	< 100 CFU/mL
Endotoxin units (EU)	< 0.25 EU/mL	< 0.25 EU/mL
Ultrapure water		
Colony-forming units (CFU)	< 0.1 CFU/mL	< 0.1 CFU/mL
Endotoxin units (EU)	< 0.03 EU/mL	< 0.03 EU/mL

* Data from AAMI (Association for the Advancement of Medical Instrumentation) 13959:2014 and ISO (International Organization for Standardization) 13959:2014.

be adhered to. It is important for a full chemical analysis of the water for dialysis to be conducted to determine the degree of water purification necessary.

The plumbing system modifications should also take into consideration the level in the home in which the dialysis is done. Should dialysis take place on higher floors, additional components, for example, pump systems and feeder tanks, may be needed to provide the necessary water pressure for the reverse osmosis unit and dialysis machine to function properly, as appropriate.

Depending on the local water conditions and regulations, other modifications like backflow preventers and blending devices may also be necessary.

Electrical Considerations Including Backup Power Supply

A stable power supply is necessary to conduct home hemodialysis. Typical electrical requirements for dialysis

machines are 115 V AC at 20 amperes. There should also be an overcurrent device installed at the service panel board equipped with a 20-ampere fuse. The dialysis machine should also be connected to a separate branch circuit that does not supply any other outlets. For locations that may experience regular power failures, a backup power supply with its accompanying equipment is recommended. The power supply should be compatible with the dialysis equipment. However, it may be necessary for an electrician to review an outlet for the machine with a dedicated circuit to the circuit breaker. Most, if not all, dialysis machines should have their own circuit breaker. It is important to take into consideration measures to manage hemodialysis in the event of power failure, for example, manual wind-back functions of the machine. Lastly, it is essential to establish the local electricial safety regulations and adhere to them.

Dialysis Machine Choice and Other Equipment

There are different dialysis machines currently available for home hemodialysis. Some offer the advantage of mobility; however, any machine, in general, is able to provide effective and good home dialysis. The choice of machine should also be tailored to the patient's individual requirements and preferences. In general, a home dialysis machine should be easy to operate and understand, as this facilitates the learning process for the patient and/or the caregiver.

The choice of dialysis machine would also determine the ease of dialysis fluid preparation. Some machines require water filtration systems, while others come with prepackaged dialysate or can generate on-line dialysis solutions.

The NxStage System One is available for home hemodialysis. To prescribe dialysis with this system, one would need to decide on the following parameters:

i. Frequency of dialysis per week, as well as the target spKt/V (per session as well as per week)
ii. Dialysate volume
iii. Dialysate composition
iv. Blood flow rate
v. Target flow fraction
vi. Ultrafiltration rate
vii. Heparin (initial bolus and additional bolus if necessary)

The dialysate volume and composition will depend on whether the PureFlow SL Dialysate Preparation System is used, or if prepackaged dialysate bags are used. The PureFlow system allows ultrapure product water to be produced from tap water, which is then mixed with the sterile concentrate to produce dialysate solution. It is available in 40–60 L preparations, while the prepackaged solutions come in 5-L bags.

A comparison of the different types of dialysis regimens is listed in Table 14.3.

A dedicated dialysis chair can be considered for home dialysis. This allows for an adjustable headrest that will allow the patient to be comfortable sitting up for the entire duration of the dialysis process and also allows the patient to recline. This should also allow the patient to assume a supine position quickly in the event that symptomatic hypotension occurs.

Space Considerations and Siting of Dialysis Machine

Patients will need storage space, for example, a cabinet/closet, to store their dialysis equipment. This includes items like needles, filters, tubing, weighing scales, etc. Some

TABLE 14.3 Home Hemodialysis Regimens

	Dialysis Regimens				
	CHD	NxStage	Short Daily Hemodialysis	Long Hemodialysis*	Long Frequent*
Frequency (sessions/week)	3	5+	5+	3–4	5+
Duration (hours/session)	4	2.5–3.5	2.5–3	>5.5	>5.5
Dialysate flow (mL/min)	500–800	400	500–800	300–500	300–500
Blood flow (mL/min)	200–400	150–200	400	200–400	200–300
Standardized K_t/V_{urea}†	2.50	–	3.75	3.75	5.83
	(12 hours/week)		(13.5 hours/week)	(26.8 hours/week)	(40.2 hours/week)

CHD, conventional hemodialysis.
* Can be performed as nocturnal hemodialysis.
† Adapted from the Frequent Hemodialysis Network analysis of solute clearance. Clearances reflect median weekly values and are model-based calculations for provided weekly treatment times
Tennankore K, Nadeau-Fredette AC, Chan CT. Intensified home haemodialysis: clinical benefits, risks and target populations. *Nephrol Dial Transplant*. 2014;29:1342–1349.

patients may also choose to store their dialysis machines when not in use. The space considerations will also determine the choice of dialysis machine and vice versa. The conventional dialysis platforms will generally be larger and less mobile, whereas users of mobile batch dialysis equipment (e.g., NxStage) will have greater flexibility in terms of choosing the dialysis location.

The choice of the dialysis room is an important component of home hemodialysis. The dialysis room should allow for the dialysis session to be conducted safely and should also allow for maintenance to be conducted regularly. It should also be uncluttered and ideally have furnishings that are easy to maintain.

The following items should be taken into consideration when choosing the dialysis room:

i. Does the patient want to conduct dialysis privately or in the same room as family members?
ii. What does the patient want to do during dialysis?
iii. The machine needs to be close to a water supply as well as drains.
iv. Is the patient doing nocturnal dialysis? If so, the bedroom would be a suitable choice for locating the dialysis machine
v. Proximity to a telephone is essential

Storage space is also necessary to house the supplies needed for the dialysis treatment. Once patients become familiar with the amount of supplies they need during a particular time period, they may be able to adjust their delivery schedule to better suit their space and storage requirements.

Water treatment units are an important component of the home hemodialysis system. The choice of the dialysis location should also take into consideration the space necessary for the water treatment unit. This area should ideally have water-resistant flooring in case of leaks and sufficient servicing and drainage access. The noise generated from the reverse osmosis unit will also need to be taken into consideration for locating the unit. The patient may also consider placing a protective vinyl sheet or a tray under the dialysis machine and water treatment unit as an additional safety measure in case of a water leak.

Hygiene and Noise

The surroundings in which the dialysis is conducted should be clean to prevent infections from occurring during home hemodialysis. Dirty clothing should be avoided during the dialysis process. Proper hand hygiene is also of importance, and proper handwashing techniques should always be adhered to, including the use of soap or alcohol rubs.

Pets may pose a hygiene problem during dialysis. In general, pets should not be allowed during the dialysis process, as they may pose both a hygiene and safety problem. Even if the pet is supervised, the pet should be kept out of the room during treatment initiation.

These hygiene requirements should extend to both the patient as well as any family member who may be assisting with the dialysis process. The participation of the family should also be assessed as part of the home visit prior to the consideration of home hemodialysis.

Safety

All dialysis machines should be equipped with monitors to detect exact arterial and venous pressures, with settings to narrow alarm ranges. The alarm type is usually sound based but may need to be light based in special circumstances (e.g., patients with hearing impairment). Leak detectors should be placed around the vascular access site, under the dialysis machine, as well as the water treatment system, to detect either blood, dialysate, or water leaks. Needles should be doubly secured with tape and plaster. For catheters, special connectors or catheter safety lock boxes can be used.

Alternative standby light sources are also necessary. Flashlights should be kept within easy reach so that the patient has an alternative light source in the event of a power failure to allow termination of treatment.

Twenty-four-hour access to the supporting dialysis care facility or technical support should be available in the event of emergencies. The relevant contact numbers for the dialysis unit and technical support should also be within easy access in the dialysis room.

Medical Staff and Technical Support

Machine breakdowns may occur, for example, due to electrical or water problems. Patients should be taught how to perform emergency dialysis termination. The dialysis unit supporting the patient should also be informed if a machine breakdown occurs so the appropriate advice can be given and the technical staff directed to the home to service the machine.

Disposal of Waste

For most patients, disposal of the effluent via the sewage system provides the best option. Appropriate drainage systems should be taken into consideration during the planning process. All sharps should be collected in a dedicated sharps container for proper disposal. The other waste can be disposed of with the general waste but should be double bagged. Recycling of plastic waste can also be considered, given that the dialysis process has a high amount of plastic waste production. The patient should check with the dialysis unit providing the dialysis support regarding any extra waste disposal requirements.

Storage of Medication

As intravenous medications, for example, erythropoietin-stimulating agents (ESAs), iron, vitamin D analogs, are administered within the home, these drugs would need to be stored in the appropriate conditions.

Conclusion

Medical and technical support is essential for the development of a home hemodialysis program and training. With proper preparation, the establishment of home hemodialysis can be facilitated safely and efficiently and allow the patient to benefit from this treatment modality.

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Recommended Reading

Tennankore K, Nadeau-Fredette AC, Chan CT. Intensified home haemodialysis: clinical benefits, risks and target populations. *Nephrol Dial Transplant.* 2014;29:1342–1349.

This review article provides an overview of the benefits, risks, as well as the possible target population for intensified home hemodialysis.

15 Vascular Access

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Introduction

It is well established that dialysis cannot be provided without access; while this should not be taken for granted, such access can be achieved in a majority of cases. In contrast, the attainment and maintenance of a single *reliable*, *long-lasting* dialysis access with *minimal complications* continue to be challenging. Achievement of such access is associated with optimal patient clinical outcomes, superior quality of life, minimal costs, and is aligned with current guidelines.[1] As such, a paradigm shift in thinking is needed and requires a focus on understanding the individual patient's short- and long-term needs as a *person* with end-stage kidney disease (ESKD).[2,3] Such a focus requires a multidisciplinary team approach where all kidney replacement therapy (KRT) options are understood and considered, in order for the patient to attain the potentially *multiple*, optimal access(es) at appropriate junctures in their ESKD lifetime. Such an approach thoughtfully considers patient transitions from one KRT modality to another, including conservative and palliative care, depending on individual needs. Clearly, the goals and abilities of a young man with glomerulonephritis as his cause of ESKD may differ from that of an elderly woman with multiple comorbidities and diabetes mellitus as her cause of ESKD; as such, these differences may be reflected in their access needs. This approach in considering the patient's ESKD Life-Plan[1] contrasts with a prior, more static approach where the goal was to attain an "ideal vascular access (VA)" for all patients for all time. Theoretically, such an ideal dialysis access would improve outcomes and limit costs, yet a "one-size-fits-all" approach may inadvertently have unintended negative consequences to both patients and health care systems. Thus, this chapter will discuss hemodialysis VA selection and review, the pros and cons, and unique clinical applications of each key hemodialysis VA, the arteriovenous fistula (AVF), arteriovenous graft (AVG), and central venous catheter (CVC). In doing so, the reader will be better equipped to consider these accesses in the context of what is appropriate for each patient at different phases of their own unique ESKD lifetime and help the patient develop an appropriate P-L-A-N. An individual P-L-A-N considers the ***P***atient's ***L***ife-Plan and corresponding ***A***ccess ***N***eeds.[1] Newer VAs on the horizon should be considered within the P-L-A-N. Further, while peritoneal dialysis (PD) is a clearly important KRT modality with its own access considerations, this chapter will not discuss PD access but will emphasize hemodialysis VA issues as they relate to a patient who may need to transfer to or from PD. Similarly, the importance of hemodialysis VA planning, creation, and maintenance in a patient transitioning from transplantation will be briefly discussed.

History of Vascular Access

The history of VA types reflects the changes in the ESKD population demographics and needs over time (Table 15.1).[4–7]

Multidisciplinary Approach to Vascular Access

Strategy and Roles

Key members of the multidisciplinary VA team include the nephrologist, surgeon, endovascular interventionalist, VA coordinator, cannulator (typically nurse or technician), and the patient and his/her support system. The planning, creation, and maintenance phases of the VA have different emphases, and as such, a different team member may "lead" where needed and appropriate. This requires mutual respect and trust among team members where clear, timely, and effective communication between health team members, the patients, and their support team are critical for successful access care. Examples of team members and roles are in Table 15.2.

The VA coordinator facilitates communication and activities across all phases. The patient and his or her support system should be engaged to participate in informed decision making during all phases.

Education

Each member of the multidisciplinary team must coordinate educational efforts so that the patient receives nonconflicting and clear information about their chronic kidney disease

TABLE 15.1 Key Highlights in the History of Vascular Access

Year	Patient Demographics and Needs	Important Influences	Key Vascular Access Development	Impact
1945	Kidney failure fatal without hemodialysis	HD was the only KRT available	Single arterial and venous cut-down for single HD	HD truly limited by access sites; short-term benefit
1960	Young patient (< 55 years old) with limited comorbidity	Ethics committee reviewed hemodialysis eligibility—provided at home	Scribner shunt	Maintenance HD became possible; infection and clotting were predominant issues
1961	Similar to 1960	Rapid access for dialysis required	First subclavian vein access for dialysis	Subclavian catheter approach became the preferred method for temporary access for the following 2 decades
1966	Young patient (< 55 years old) with limited comorbidity	Individuals with diabetes were not eligible for dialysis	Cimino-Brescia fistula	Longer patency and reduced complications; Primary failure rate < 15% in original fistulas
1970	Patients with lack of or exhaustion of peripheral vessels; pediatric hemodialysis population with small vessels	A new method of access besides a shunt was required	Prosthetic graft	Thrombosis, infection remained a problem (as in shunts); aneurysms were linked with repeated cannulation
1973	Patients with diabetes and/or with greater comorbidities	Patients of all ages and etiologies of ESKD became eligible for dialysis	Prosthetic graft	Search for synthetic and biological materials that would improve patency and reduce complications began and is ongoing
1993	As earlier	Need for repeated catheter insertions in the same patient	Chronic central venous catheter (CVC)	Long-term HD with indwelling CVC possible
1994	As earlier + more home nocturnal dialysis patients		Uldall-Cook central venous catheter	Patients were able to provide dialysis of long duration overnight at home
2013	As earlier	Increasingly older patients with greater comorbidities and living longer; exhaustion of vascular access options and central venous occlusion	HeRO graft; a hybrid between synthetic graft (arterial component) and CVC (venous outflow)	Bypasses the central occlusion with the CVC portion and allows peripheral access via graft portion. Combined risks of graft and CVC exist, diligent care required.
2014	As earlier		Endovascular AVF created percutaneously	Two devices (WavelinQ and Ellipsys) using novel techniques (magnetic catheters with radiofrequency energy and thermal resistance devices, respectively) for AVF creation
2016	As above		Bioengineered vessels for AVG	

AVF, Arteriovenous fistula; *AVG*, arteriovenous graft; *ESKD*, end-stage kidney disease; *HD*, hemodialysis; *KRT*, kidney replacement therapy.

TABLE 15.2 Hemodialysis Vascular Access Team Members and Primary Roles

	Lead Team Member	Phase	Role	
Vascular Access Coordinator	Nephrologist	Before VA created	Medical eligibility and timing of KRT modality and vascular access: evaluates comorbidities, functional status, life circumstances and goals; establishes ESKD Life-Plan with the patient	Patient and support system
	Surgeon	Before VA created	Surgical eligibility of vascular access: vessel assessment +/- mapping	
	Surgeon or interventionalist	VA creation/ insertion	Creates AV access* (fistula or graft) or inserts catheter	
	Nephrologist surgeon	After VA creation	Assesses for development, complications, and readiness for use	
	Surgeon or interventionalist	After VA creation	Facilitates or rectifies access issues in order to attain and/or maintain patency (e.g., AVF revision, AVG angioplasty, CVC exchange)	
	Cannulator nephrologist	After VA creation	Assesses for readiness of cannulation Monitors for dialysis related complications	

* In this chapter, AV access refers to fistula or graft.
AV, Arteriovenous; *AVF*, arteriovenous fistula; *AVG*, arteriovenous graft; *CVC*, central venous catheter; *ESKD*, end-stage kidney disease; *HD*, hemodialysis; *KRT*, kidney replacement therapy; *VA*, vascular access.

(CKD), modality options, and the associated access. When patients and their family members are active participants in the decision-making process, adherence greatly improves.[8,9] Optimal outcomes, such as initiating hemodialysis with a functioning access, are more likely when patients and their families receive high-quality, individualized CKD education.[10,11] For example, in a nationwide study of >3000 patients, patients who received education about VA had a twofold higher odds of having an AVF or AVG placed compared with a CVC. Patients who receive education about VA also had lower anxiety about receiving their AVF.[12]

A key element to emphasize in the education of hemodialysis VA is to preserve veins by protecting them against venipunctures, intravenous lines, central venous catheterizations, and pacemaker insertions on the side of the planned future hemodialysis VA.[13] For example, when venous access is required, only the dorsal aspect of the hand should be used. Peripherally inserted central catheters ("PICC lines") should be avoided in patients with a potential future hemodialysis need and should be considered absolutely contraindicated in patients with stage 4–5 CKD.[14] Patients already undergoing hemodialysis can have blood draws done during their hemodialysis session to preserve veins.[15] Importantly, adequate arterial inflow is necessary for AVF maturation and prolonged patency. There has been a recent increase in the use of radial arteries as wrist access for cardiac interventions; such interventions may cause complications and damage arteries, limiting future lifelines for CKD patients.[16,17] Alternate access, such as via femoral catheterization, should be used in CKD patients who may need VA in the future. Regardless of the CKD stage, each patient should have a vessel preservation plan.[1] This emphasis on vessel preservation, as well as other important VA education, must be supported by health care workers and administration within the hospital or dialysis facility in order for it to be effective. Optimal patient outcomes and lowered costs will reinforce the effectiveness of comprehensive modality and access education.

Planning and Choice of Vascular Access

Dialysis access planning should start in CKD stage G4 (glomerular filtration rate [GFR] 15–30 mL/min) or in the "red" area of the risk map of CKD prognosis (Kidney Disease: Improving Global Outcomes [KDIGO] staging system[18]), when education about CKD and modalities of KRT should be discussed. The rate of decline of GFR over time is perhaps the best predictive guide to timely referral and access placement. Recently, a CKD progression prediction model was developed and validated[19]; this model and the patient's degree of proteinuria may help estimate the progression of CKD to ESKD and planning for dialysis access.[20] The components required for patient-focused access planning are:

1) Timely and appropriate referral;
2) Education (above);
3) Patient history and physical exam; and
4) Supportive investigations.

Timely and Appropriate Referral

Timely referral to a nephrologist and access surgeon or interventionalist (herein referred to as access "operator") for CKD management and evaluation by an operator, respectively, increases the likelihood for placing a native vein AVF and reduces the likelihood of temporary CVC placement. Therefore, when GFR approaches 30 mL/min (CKD Stage G4), patient education about CKD, its potential progression to require KRT and dialysis access must begin. In terms of the GFR, "sweet spot" for arteriovenous (AV) access creation, this will depend on the patient's age, rate of CKD progression, and prognosis. For example, elderly patients have a slower rate of GFR decline, lower incidence of ESKD, and higher mortality rate and may suffer from an unnecessarily high ratio of unnecessary to necessary AV access surgeries and interventions.[21,22] Clinicians should aim to reduce the number of unneeded procedures to attain functioning necessary AV accesses. An approach to access creation is illustrated in Fig. 15.1.

Patient and Vascular Access History

A "hemodialysis access–focused" history is unique and required in planning dialysis access. Such a history will shed light on potential complications that may occur, such as failure of an AVF to mature, potential for high cardiac output failure or AVG-associated steal syndrome, and will navigate the access operator to either preemptive intervention or consideration of an alternate access. This "vessel-focused" history includes determining the type and nature of past access procedures (especially CVCs, PICC lines, and pacemakers), past accesses (interventions required to facilitate or maintain its patency and reason(s) for loss), breast and axillary dissection surgery, chest radiation, and emergency vascular cut-downs. Furthermore, a parallel "PD-focused" history should be pursued to help inform the choice of dialysis access. Factors that may affect the peritoneum, such as the presence of significant prior abdominal surgeries, may lead one to exclude PD and focus on hemodialysis VA.

Physical Examination

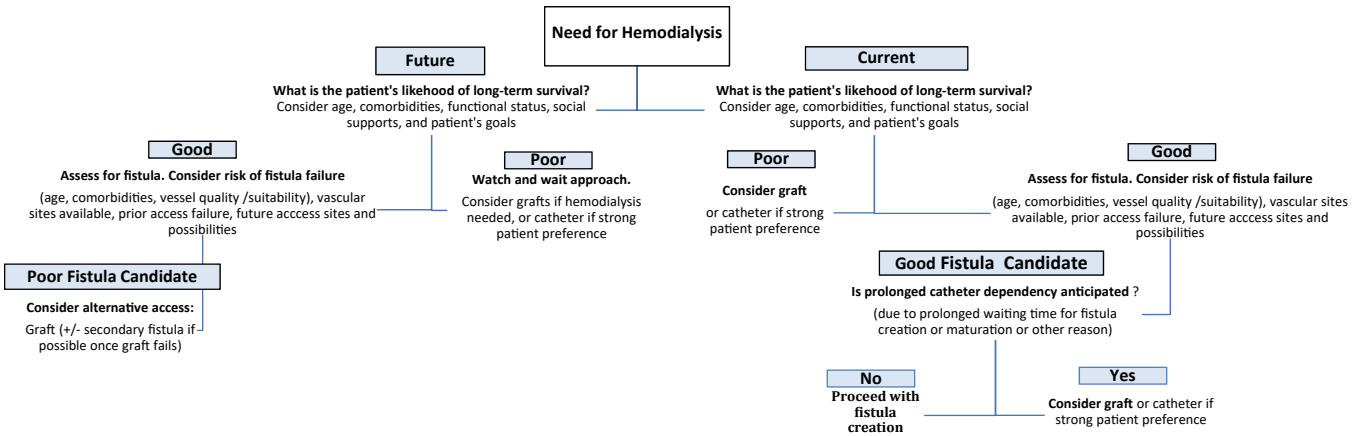
The focused physical exam includes a detailed inspection of the neck, chest, abdomen, and extremities. The examination must take into consideration the significance of previous chest and abdominal surgeries (for PD), pacemakers, presence of edema, and collateral vein formation that may suggest central vein pathology. The vascular examination must assess both the arterial and venous systems.

The hemodialysis VA exam requires a relaxed patient in a comfortable environment. A cold room will cause vessel vasoconstriction and potentially underestimate the size of available vessels. The use of an upper arm tourniquet or warming the extremity (e.g., with hot water), followed by asking the patient to close and open their fists, will help augment vessels for assessment.[23] The arterial assessment includes evaluation of pulse quality, segmental blood pressure, and the Allen test.[24,25] The venous system comprises a detailed inspection and palpation for vessel integrity, caliber, and size. Duplex ultrasound may be used to clarify or confirm concerns of vessel integrity and/or may be used to better define surgical and interventional anatomy.

Supportive Investigations

Duplex ultrasound is particularly useful in the obese patient but may not always add much to a careful and experienced physical exam (see later).[26,27] Indeed, the quality of the duplex ultrasound examination is operator dependent; ideally, the surgeon should perform the duplex ultrasound or be present to direct the sequence of examination steps and mark the skin, documenting vessel size, intended surgery sites, and anatomical variations.[28] The specific features assessed during duplex ultrasound are listed in Table 15.3.

Since duplex ultrasound findings need to be considered within the context of the other variables determined by the history and physical exam, using size criteria alone to determine vessel eligibility for the desired access should be avoided. Doing so may lead to missing other important features of the vessel, including vessel quality (calcifications, distensibility), and prior vessel injury that may contribute to neointimal hyperplasia and VA failure. Imaging must



• **Fig. 15.1** Algorithm for Considering Vascular Access Choice.

TABLE 15.3 Main Features Addressed by Duplex Doppler Vascular Examination

Arterial System

- Integrity and/or size of the artery from the axilla to hand including the palmar arch.*
- Dual arteries in upper arm, i.e., high bifurcation.
- Degree of arterial wall calcification.
- Arterial stenotic lesions.
- Blood flow at defined segments.

Venous System

- Detailed venous anatomy in arm and leg as needed.
- Vein size mapping from wrist to axilla.
- Vein patency and presence or lack of stenosis.
- Patency and flow pattern of subclavian vein.
- Presence of diving venous branch at antecubital fossa.

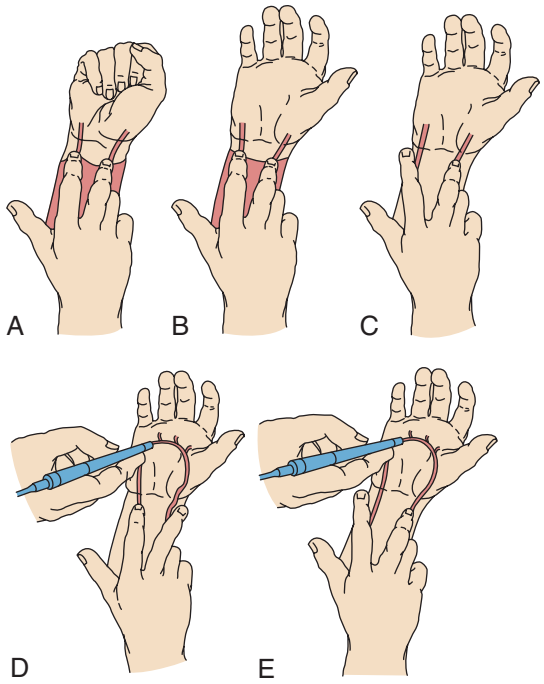
* A (radial) artery diameter of 2 mm or less is unlikely to mature to provide prescribed hemodialysis in North America and therefore fail from inadequate fistula flow (less than 500 mL/min). Likewise, a venous diameter of 2.5 mm or less at the time of anastomosis is likely to yield inadequate flow rate. Note that the Doppler characteristic of high arterial flow resistivity prior to the creation of a hemodialysis access should change to hyperdynamic low resistive characteristics after creating the access.

document full compressibility and patency of all vessels examined with absence of any luminal defects and/or thrombosis. Outcomes are expected to be superior when duplex ultrasound involves maneuvers to assess the vessel's characteristics, especially when directly observed by the operator performing the access surgery; however, this speculation requires proper study and confirmation.[1]

The Allen test can be performed during duplex ultrasound to confirm findings found by physical exam. A photoplethysmography probe is used to obtain the baseline thumb arterial flow Doppler signal without any compression maneuvers. The signals are then obtained repeatedly while manually compressing the radial artery first, the ulnar artery next, and then both arteries together. If the Doppler signal demonstrates a significant reduction in the amplitude when the dominant artery is compressed, i.e., both palmar arches do not communicate (Fig. 15.2), this should serve as a warning of risk for hand ischemia after access placement.

Alternatively, a modified Allen's test may be performed. This is done by identifying the radial artery at the wrist and/or at the dorsum of the hand (posteriorly between the bases of the first and second metacarpals). The radial artery is compressed proximal to this site to occlude flow during insonation using spectral and color Doppler imaging. Reversal of blood flow distal to the proximal occlusion confirms patency of the palmar arch.

The value of preoperative vessel mapping has ranged from harmful (leading to delays in access creation and greater failures),[29] equivocal (similar outcomes to physical exam),[26,30] and superior with improved fistulas outcomes.[31] Given the range of potential outcomes, current use of preoperative vessel mapping to assist with AV access planning and creation is not mandatory, largely dependent on the patient's characteristics and the experience of the performing and interpreting physician.[1]



• **Fig. 15.2** Allen's test is used to determine whether the arterial supply of the hands is adequate and whether the hand arch connects the ulnar and radial arteries. Arteries should not be ligated or occluded during an access procedure if the Allen's test shows poor collaterals.

Angiogram. If the physical exam or duplex ultrasound assessment raises concerns where confirmation or clarification of vascular anatomy is warranted, invasive imaging using contrast dye or CO_2 angiography (as appropriate) is warranted. 10–15 mL of dilute contrast dye has not been associated with accelerating the decline in GFR.[32,33]

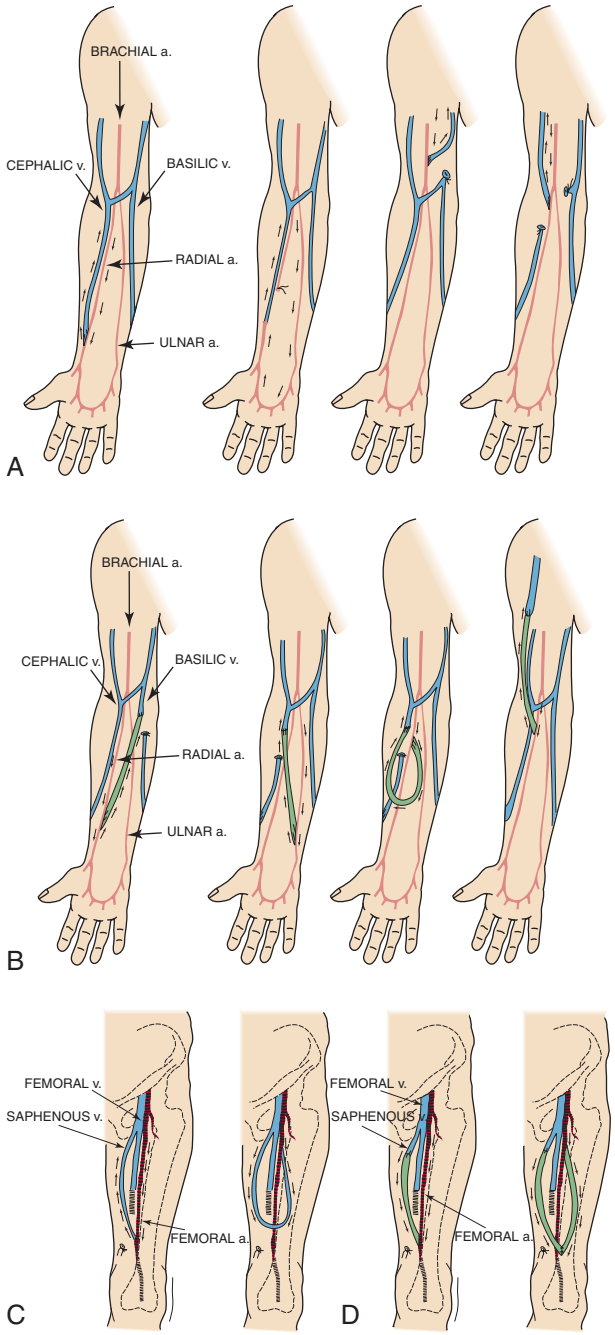
Access Site Locations

In considering VA location, there should be a carefully thought-out, systematic progression from one VA site to another. With few exceptions, there should be an attempt to preserve and use every site available to extend the patient's ESKD "lifeline." An "upper extremity first" followed by a "distal to proximal" approach maximizes potential access sites and takes advantage of the dilatation effect of access procedures on the vasculature; this may lead to the development of veins and arteries at sites that were initially deemed suboptimal.

Upper extremity

Fistulas

Fistulas are relatively simple to create, and different types of autogenous artery-vein anastomosis are possible, including



• **Fig. 15.3** Optimal Progression of Access Procedures. The optimal progression of access is from the nondominant upper extremity distally to proximally, using autogenous veins (A). Next, the dominant arm should be used. Once all autogenous veins have been exhausted, prosthetic graft should be used in the same progression (B). When upper extremity access sites have been depleted, the lower extremities can be used (C = autogenous fistula; D = prosthetic graft). The progression suggested is based on the durability of the conduit and likelihood of complications such as access thrombosis, steal syndrome, and infection.

end-to-side (end of the vein to side of the artery), terminalized side-to-side, laterolateral, and end-to-end (Fig. 15.3A).

Wrist

Snuffbox radio-cephalic fistula: is an anastomosis between the distal radial artery and cephalic vein (between the tendons of the extensor pollicis brevis and extensor pollicis longus in the anatomical snuffbox).

Forearm

Radio-cephalic fistula: the Brescia-Cimino fistula connects the radial artery to the cephalic vein.

Radio-basilic transposition: the basilic vein in the forearm is also an excellent conduit for hemodialysis, although it needs to be transposed to the radial region for accessible cannulation and good function. Mobilization of the basilic vein with retunneling is a good alternative when the cephalic vein is not available in the forearm.

Upper Arm

Brachio-cephalic (a variant is the Graz fistula): a brachial artery to cephalic vein anastomosis or brachiobasilic: brachial artery and transposed basilic vein anastomosis

Special Circumstances

- Veins with adequate diameter but inadequate length: the addition of harvested veins, such as saphenous veins, can be used to provide extra length if required (as in transposed fistulas) and is an option, although rarely performed. Tunneling and transposition of veins may allow the approximation required to create an AV anastomosis.
- Deep veins with inadequate diameter: a two-stage approach can be used in this situation. The first stage is to connect the artery and the vein. A period of time is given to allow the vein to "arterialize" or mature. If successful, the second stage is to transpose the matured vein to a subdermal location to allow for cannulation.

Grafts

An AVG is a prosthetic interposition between an artery and a vein. Grafts are typically categorized as synthetic or biologic. There are a variety of graft materials, types, and configurations (Fig. 15.3B).

Wrist

Straight forearm: a straight graft from the radial artery to the median cubital vein.

Forearm

Loop forearm: a loop graft connecting the distal brachial artery or proximal radial artery to the median cubital vein.

Upper Arm

Straight or curved upper arm: grafts of various configurations can connect the brachial artery with the basilic, brachial, or axillary vein.

Central Venous Catheters

Catheters are typically used in urgent or emergent situations that require hemodialysis. In such situations, the CVCs are typically noncuffed and nontunneled. However, they may also be cuffed and tunneled within the subcutaneous tissue to reach the target vein. The right internal jugular vein is

TABLE 15.4 Suggested Order of Location for Central Venous Catheter Placement

Preference	Vein	Comments
1	Internal jugular*	Right side preferred
2	Femoral vein	Ensure adequate catheter length
3	Subclavian	Lowest infection risk of all locations
		Trendelenburg position during insertion may decrease the risk of air embolism
		Only use if no further access is possible on that extremity
4	Lumbar	A location of last resort when no other access site available.

* In a patient who is anticipated to require long-term dialysis, it may be preferable to use the femoral vein as the first choice in order to preserve central veins in the neck for future AV fistula or AV graft creation. Stenosis of internal jugular veins is more common than previously indicated (up to 30% or more) and may rival the rate of central stenosis found with subclavian veins. However, the risk factors, timing, and onset of central stenosis are currently not well understood. This approach to preserve neck veins is particularly important to consider in patients with good prognosis and/or an expected long-term survival (particularly if they are not transplant candidates). These patients would benefit from an AV access, but this may not be possible if a CVC in the internal jugular vein caused central vein stenosis, preventing successful AV access creation on the side of the CVC.
AV, Arteriovenous; *CVC*, central venous catheter.

preferred to the left internal jugular vein due to a more direct route to the right atrium. Subclavian vein catheters should be avoided due to their high risk of central vein stenosis. The CVC tip should be placed in the mid–right atrium. After insertion, the position should be checked by a chest x-ray in the upright position as the catheter has a tendency to retract 3–5 cm when the patient moves from a supine to an upright position. The order of preference of CVC location is indicated in Table 15.4. Regardless of location, all insertions should be guided by imaging (ultrasound if it is a bedside nontunneled CVC insertion or under fluoroscopy if it is a tunneled CVC),[1] using the Seldinger technique. It is important to use a dilator over the guidewire before inserting the catheter to minimize vessel trauma. Trauma to vessels increases the likelihood of central vein stenosis.

Lower Extremity

Femoral Region

When all upper extremity sites have been exhausted, lower extremity access (primarily femoral) may be the only option. As with upper extremity access, lower extremity access is dependent on adequate arterial inflow and unobstructed outflow in a good quality vein. In such cases, AVFs and AVGs can be constructed in a similar manner to that of the upper extremity (Fig. 3C,D). Due to the higher flow rates through femoral vessels, there may be greater risk of steal syndrome. There is also the potential risk of greater bacterial colonization and infection; careful access care using aseptic technique is required regardless of the location, but special care is required in situations that put patients at high risk of access infection in the femoral region, such as diarrheal illness.

CVC can also be placed in the femoral region. Temporary requirements (e.g., when dialysis is needed while an AV access is being declotted) typically involve an uncuffed, nontunneled femoral catheter that can be removed immediately after the dialysis session. More prolonged use requires the insertion of a cuffed, tunneled catheter. A randomized controlled trial and several meta-analyses have demonstrated equivalent thrombosis and infection rates using tunneled femoral catheters compared with internal jugular catheters.[34–36] However, except when there are no other available access options, femoral catheters should be used only for limited timeframes and only when necessary.

Unusual Locations

Axillary-Axillary/Femoral-Popliteal

When all conventional access sites have been exhausted, the access operator must be creative to obtain a VA for long-term hemodialysis. Connecting an available and adequate large artery to any acceptable outflow vein can, in necessary situations, result in a functional VA for long-term hemodialysis. It is critical *before* a dialysis access is created to consider the "contingency and succession plan," i.e., what corrective options are available for the patient in case of complications and/or what *type* and *where* the *next access* will be created, respectively.[1] Having a comprehensive and thoughtful access creation plan, contingency plan, succession plan, and vessel preservation plan are key components supported by national guidelines.[1]

Overall Clinical Considerations

Fig. 15.1 provides an algorithm to assist in the clinical approach to a patient who needs VA.

Once the HD access is created, it should be routinely monitored by physical examination.[1] The presence of a palpable thrill, pulse quality, and appearance of the overlying skin (i.e., redness, edema, skin quality) are essential components of the examination (see "On Dialysis Rounds," later).

This approach encompasses patients who have established CKD or ESKD. However, the patient who requires emergent or urgent hemodialysis deserves a separate discussion.

Patient Requiring Emergent Dialysis

Patients may require emergent hemodialysis to limit or prevent life-threatening complications such as hyperkalemia, pulmonary edema refractory to medical management, uremic seizures, uremic pericarditis, and uremic bleeding—especially prior to required surgeries. If such a situation arises and the patient is without a usable AV access, the only alternative is to provide temporary access for hemodialysis. In most cases, a temporary uncuffed femoral catheter is the most appropriate access. After dialysis has been completed, more longer-term access can be discussed, if required. Again, the focus is on saving central veins if the patient is anticipated to require long-term hemodialysis in the future.

Urgent Patient

The urgent start patient is typically a CKD patient who is in one or more of the following common situation(s): (1) a patient with established CKD with stable GFR who suffers an unexpected medical event that destabilizes the previously stable GFR; (2) a hospitalized patient who develops or has newly diagnosed ESKD; and (3) a patient who arrives in the emergency room for unrelated reason or with non–life-threatening symptoms, previously undiagnosed but has ESKD. Other situations exist; however, the common factor is that the patient does not fit the criteria of "emergent" dialysis and has limited time (1–3 weeks) before dialysis becomes necessary. These urgent start patients account for 30%–50% of new starts to dialysis. These patients deserve time to consider their ESKD Life-Plan[1] before rushing in to put in a temporary CVC access. Again, the principle is to preserve future access sites. All KRT modalities should be considered; if PD is appropriate, an "acute" PD catheter can be inserted by the surgeon, interventionalists, or at the bedside by the nephrologist.[37] If hemodialysis is appropriate, an early cannulation graft can be placed and used within 72 hours.[1] If this is placed in the forearm, it will avoid unnecessary central vein damage by a CVC to facilitate future AV access success. Once the graft becomes problematic, a fistula can be created by the cephalic vein developed by the graft.[38] On the other hand, if the access operator assesses that an AVF can be created and matured within the timeframe before dialysis is required, or within a reasonable time period without resulting in prolonged catheter dependence, an urgent AVF creation is appropriate. This requires the coordinated teamwork and education discussed earlier.

Advantages and Disadvantages of Each Vascular Access Type

Fistula

Advantages of Arteriovenous Fistula

The undisputed benefit of a matured, carefully cannulated functioning fistula is that it can provide reliable, longstanding access for hemodialysis with minimal complications. By extension, such a fistula should then offer the patient high satisfaction, good quality of life, and be cost effective.

The minimal vascular requirements for a successful AVF are listed here.

Minimal Vascular Requirements for Successful Arteriovenous Fistula

1. Absence of central vein obstruction.
2. Segmental blood pressure differential of less than 20 mm Hg.
3. Lack of segmental stenosis of artery or vein.
4. Anastomosis luminal diameter of at least 2.5 mm.
5. Straight vein cannulation segment of at least 6–8.0 cm.
6. Vein cannulation segment less than 5 mm below skin surface.
7. Matured vein diameter of at least 4 mm.
8. Flow rate of 500 mL/min or more (for typical North American dialysis patient and prescription)

At 4–6 weeks after creation, if the AVF has not dilated to 4 mm or has a blood flow of >500 mL/min, the AVF should be investigated (e.g., duplex US or fistulogram) to identify correctable culprits, such as stenotic or collateral vessels that may be limiting flow through the vein.

Disadvantages of Arteriovenous Fistula

The most frequent AVF complications include maturation failure (20%–60%), thrombosis, aneurysm formation, and steal syndrome. Fistula infections are uncommon but vary with cannulation techniques. Buttonhole cannulation is associated with higher risk of infection and associated serious complications (septic emboli and metastatic seeding, e.g., endocarditis, osteomyelitis; infected mycotic aneurysms, fistula loss).[39–41] Buttonhole cannulation should only be used in special circumstances,[1] such as those with short or limited cannulation length, convoluted and/or large aneurysmal fistulas, and ideally should be self-cannulated by the patient themselves.

Graft

Advantages of Arteriovenous Graft

Grafts have a lower early failure rate in comparison to AVF and can be used soon after creation. The "early cannulation grafts" can be used within 24 hours of creation, while the standard grafts can be used 2–4 weeks after creation (depending on extremity swelling).[42] Equivalent cumulative patencies, infection, and intervention rates compared with AVF can be achieved.[1,37] Thus, in subsets of populations where AVFs are not possible, an AVG is a reasonable alternative.[1]

A variety of synthetic and biologic materials can be used and/or are in development. Examples of synthetic compositions include expanded polytetrafluoroethylene (ePTFE) and variants (trilaminate compositions, polyurethaneurea and siloxane additives, elastomeric membranes, heparin bonding, etc.) and Dacron. Examples of biologic material–based grafts include bovine heterografts, bovine mesenteric

vein, cryopreserved saphenous vein, human umbilical vein, and engineered human extracellular matrix compositions. There are a number of graft types (straight, tapered, spiral) and configurations that can be placed within the body (straight, loop, curve). Grafts can connect two vessels that may not otherwise be possible due to their distance. Thus, a graft can be used for almost any patient if they have acceptable receiving vessels.

Disadvantages of Arteriovenous Graft

The most common complication of AVG is the development of neointimal hyperplasia that leads to recurrent stenosis and thrombosis. Multiple agents have been used to reduce stenosis and thrombosis, such as warfarin, dipyridamole, sulfinpyrazone, ticlodipine, aspirin, dypyridamole and aspirin (Aggrenox), and fish oil. Only dipyridamole/aspirin and fish oil have been found to be effective in reducing thrombosis and improving graft patency in randomized controlled trials.[43,44] Other agents have either been ineffective or had a signal for harm (e.g., serious bleeding with warfarin). When hemodynamically significant stenosis (typically evidenced by clinical signs or symptoms—see "On Dialysis Rounds" later) or thrombosis occurs, corrective endovascular or surgical intervention is required to maintain or salvage graft patency.

Another important complication is infection. Previously, grafts have been shown to have a significantly greater infection risk than fistulas (up to 10-fold higher), but more current data have shown equivalent infection risk.[45,46] This may be due to more consistent perioperative antibiotic coverage, better attention to hygiene by patients, and use of aseptic cannulation techniques by cannulators. Indeed, graft infection is a modifiable complication, and every effort should be made to avoid graft infection (Chapter 19).

Lastly, pseudoaneuryms and aneurysms result from poor cannulation, such as "one-site-itis." Typically, pseudoaneuryms are resected when they reach a diameter two times greater than the graft width or increasing in size. Vascular steal syndrome and monomelic neuropathy are less common but serious complications, often necessitating ligation of the graft.

Central Venous Catheter

Advantages of Central Venous Catheter

CVCs are widely available, can be quickly and easily inserted into various sites in the body, and can be used immediately for hemodialysis. There are a variety of CVC materials and configurations. The two most commonly used materials are silicone and polyurethane; both are biocompatible and durable. In an attempt to reduce bacterial colonization or improve flow, catheters have been coated with antimicrobial agents and anticoagulants; however, their effect typically dissipates by 2–3 weeks.[47] There are a variety of port and tip designs to assist in reducing recirculation.[48] Many catheters can provide excellent blood flow rates of >350 mL/min. Many patients like the convenience of catheters without the need for two-needle cannulation or the need to wait for hemostasis after dialysis has been completed.[49] Some patients prefer catheters because they do not have the cosmetic disfigurement that can occur with fistulas or grafts and can hide the catheter under their clothing.[9,50]

Disadvantages of Central Venous Catheter

Catheters are the VA type associated with the greatest risk of complications, often leading to significant morbidity, hospitalizations, and mortality.[51] Complications can be short-term (around the time of insertion: 5%–15%) or long-term. Short-term insertion-related complications include arterial puncture, cardiac/pericardial puncture, hematoma, hemothorax, air embolism, pneumothorax, infection, malposition, mechanical problems, and malfunction (catheter kinking or fracture; intraluminal thrombosis). Long-term complications include infection (see chapter on VA infections), thrombosis, and stenosis of veins. Due to the serious consequences of catheter use, cuffed tunneled CVC use should be limited to the following situations:

- Exhaustion of all options to create an AV access (AVF or AVG), as determined by a qualified surgeon/interventionalist
- Use as a bridge access until an already created AVF or AVG matures
- Use as a bridge access until the time of a *scheduled* donor kidney transplant (within a reasonable time frame determined by the facility, e.g., 6 months)
- Use as a bridge when a patient requires hemodialysis due to a complication from PD (e.g., "resting" of the peritoneal membrane after an episode of peritonitis or in delayed graft function in a patient with a newly transplanted kidney)
- Limited life expectancy

Due to some of the perceived benefits of catheters, some patients have a personal preference for CVC as their access of choice.[52] However, it should be documented that the patient understands the risks of prolonged CVC use, especially when an alternate AV access (AVF or AVG) is available. The benefits of other AV access and their availability as an option should be made clear to ensure informed consent to using the CVC.

On Dialysis Rounds

Key Physical Exam Findings Indicative of Access Problems

- Swelling of the face, chest wall, shoulder, breast, or neck may be indicative of high venous pressure suggestive of central stenosis (e.g., superior vena cava or innominate vein). Collateral veins may also be evident on physical exams.
- Localized edema is indicative of potential infection or venous outflow impairment; e.g., isolated forearm edema suggests a stenosis in the main draining vein.

- Palpably increased access pulsation: may be predictive of venous anastomotic stenosis and/or stenosis in the access body.
- Palpation may detect fibrotic stenotic lesions; e.g., a "step" can be felt at the anastomosis.
- An overly strong (water hammer) pulse may be detected upstream to a stenotic lesion. The access downstream to the stenosis may collapse on arm elevation.
- High bruit pitch and/or short diastolic component may indicate stenosis; recall bruit should be heard throughout systole and diastole.
- Reduction in bruit intensity following arm elevation is indicative of arterial inflow abnormalities limiting flow.
- Prolonged bleeding time after needle withdrawal of >10 minutes or a change from current baseline with no change in anticoagulation: This should be measured and documented as a potential indicator for AVF or AVG stenosis and requires evaluation.
- Evidence of aneurysms or pseudoaneurysms, thinning of the skin over the access, superficial ulcers.

Dialysis staff should be aware of key findings indicative of access dysfunctions—such findings should be promptly brought to the rounding nephrologist's attention. Similarly, nephrologists should themselves be vigilant in order to follow up with appropriate investigations or corrective procedures in a timely manner. Depending on how regularly a nephrologist rounds, part of or an entire dialysis round should be dedicated to identifying and evaluating VA-related issues. However, one should be mindful that the assessment of access stenosis might be problematic when the patient is connected to the hemodialysis machine. Thus, arrangements should be made for proper access evaluation when the patient is off dialysis.

The previous hemodialysis VA strategies and decision-making processes require a coordinated teamwork approach that encompasses a "continuum of care" model for CKD. The dialysis access strategy is part of the patient's P-L-A-N and is consistent with their "Life-Plan" whereby the appropriate access is the one that aligns the modality for KRT (dialysis or transplant) to help each patient achieve his or her life goals safely.[1] As such, a dialysis access short- and long-term plan should be updated on a regular basis.[1] With a proactive approach, future anticipated access problems can be addressed with the overall goal to avoid access complications, dialysis interruptions, temporary CVC use, and associated morbidity.

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Cannulation of Arteriovenous Vascular Access: Science and Art

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Introduction

The delivery of hemodialysis (HD) therapy for a patient with an arteriovenous (AV) vascular access is dependent on successful vascular access cannulations. A typical in-center HD patient requires routine cannulation for 156 treatments per year. Despite the high frequency of cannulation, limited randomized controlled trials (RCTs) provide the scientific aspect. The art of cannulation is the skill part of the procedure. Nephrologists oversee the overall care, including cannulation. Nephrology nurses and nephrology clinical technicians provide direct patient care, including initial and routine cannulation.

Access Monitoring

The simple One Minute Check should be performed before every HD access cannulation. A Fistula First Work Group created the One Minute Check. It mimics the simple cardiopulmonary resuscitation (CPR) check of "look, listen, and feel" before starting CPR. The simple check can avoid the cannulation of thrombosed access. Cannulation of thrombosed access may lead to bleeding at the puncture site during the thrombectomy procedure. Assessment of the access must occur before cannulation. The simplification of the check was intentional to allow the patient, family or care partner, and patient care technicians to perform the check. In the United States, the technician may be restricted from making a clinical assessment but can perform a check. Normal findings are a green light to process with the cannulation procedure. Abnormal findings are considered a red stop sign to pause the cannulation and escalate to the registered nurse. The nurse can then utilize the expert level One Minute Check for additional assessment. The expert level is an expanded check that includes the augmentation test at the expert level for the dialysis care team members—including the nephrologist and advanced practice team members. State laws for the scope of practice vary by state.

The 2019 Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Vascular Access 2019 Statement: Vascular Access General Monitoring 11.1 KDOQI considers it reasonable to assess or check the vascular access prior to every cannulation (if AV access) or connection (if central venous catheter [CVC]) for potential complications. Refer to Table 16.1.

The patient One Minute Check version is available for AV fistula (AVF), AV graft (AVG), and HD catheters. The One Minute Check is intended for the patient/family/care partner to do daily and to report any abnormal findings to the dialysis care team.

The Augmentation Test is at the expert level and is a simple, noninvasive means of detecting an inflow issue. A common cause of a new AVF to fail to mature is the development of juxta-anastomotic stenosis that develops just above the anastomosis. The stenosis inhibits the access flow and thus reduces the main fistula outflow vessel dilatation.

The novice and expert One Minute Check tools (AVF/AVG/catheter) are available online at https://esrdncc.org/en/resources/lifeline-for-a-lifetime/step-eight-the-one-minute-access-check/

The development of outflow stenosis in the AVF or AVG can trigger the sequel of lowered access flow, increase in venous pressures, decrease in the internal access flow, occurrence of recirculation, and reduction in the dialysis adequacy.

The patient/care partner can detect changes in the bruit and thrill by using the daily One Minute Check. The dialysis team members can detect changes in the bruit and thrill by utilizing the One Minute Check prior to each cannulation. Anytime a change is detected, the access should be evaluated with the expert level One Minute Check without the needles inserted. The expert can then determine if the access is useable to initiate the dialysis session. A spot assessment of the clinic-specific policy and procedure for the full monitoring and surveillance can be utilized to confirm the One Minute Check findings. The monitoring and surveillance can include measurement of the access flow, recirculation, review of venous pressure, prepump negative pressure, inability to achieve the prescribed blood flow rate, and/or prolonged bleeding post needle removal, as a few examples (Table 16.2).

TABLE 16.1 KDOQI Physical Examination (Monitoring) Related Practice Guidelines

13.1 KDOQI recommends regular physical examination or check of the AVF, by a knowledgeable and experienced health practitioner, to detect clinical indicators of flow dysfunction of the AVF. (Conditional/Strong Recommendations, Moderate Quality of Evidence)

13.2 KDOQI recommends regular physical examination or check of the AVG, by a knowledgeable and experienced health practitioner, to detect clinical indicators of flow dysfunction of the AVG. (Conditional/Strong Recommendations, Moderate Quality of Evidence)

13.3 KDOQI considers it reasonable for nephrology trainees and health practitioners involved with clinical HD patient care to be properly trained in physical examination of the AV access to monitor for and detect AV access flow dysfunction. (Expert Opinion)

AV, Arteriovenous; *AVF*, arteriovenous fistula; *AVG*, arteriovenous graft; *HD*, hemodialysis; *KDOQI*, Kidney Disease Outcomes Quality Initiative.

General Process of Care Related to Cannulation

The process of care for HD varies significantly by geographic staffing patterns. The U.S. staffing pattern is highly dependent on the direct care role of the patient-care technicians. The minimum qualifications for technicians include a high school diploma. The training is on-the-job training. The nurses direct the care delivered by technicians. Care includes cannulation, the procedure to initiate HD, monitoring HD treatment, and the procedure to terminate HD treatment. Outside the United States, the role of technicians is limited. Direct care is typically provided by nurses. The ratio of staff members to patients also varies significantly by geographic location. Sample staff patterns in the United States may be one nurse to several technicians, with one technician assigned to cover three to four patients each. The skill level of nurses for cannulation is commonly limited as the nurses are mainly dealing with patient assessments and HD catheter care (in states that prohibit technicians from initiating/terminating the HD treatment). Thus, the local practice patterns determine the vascular access and cannulation process of care.

Staff is assigned time for different procedure steps to initiate dialysis treatment for a single patient. The time allotment often does not include additional time for assessment of the vascular access or troubleshooting of the cannulation procedure. The staff member is expected to complete the dialysis initiation procedure within the time allotment and then move to the next patient. Should the staff member exceed the time allotment with one patient, initiation of dialysis for the subsequent patients can be delayed. The snowball effect of delays commonly leads to staff stress and patient frustration and is a common root cause of negative patient and staff interactions.

The initial vascular access cannulation can exceed the typical time allotment of the dialysis initiation per patient. The staff assignment needs to be adjusted to allow the staff to take the extra time required to cannulate the vascular access successfully. Patients fear of needles and stress triggered by their first-ever cannulation procedure may require additional emotional support from the care team. One suggestion can be to move the patient with the first-ever cannulation to be the last patient assignment for the staff member of the specific shift. The change in time can allow for a more extended time allotment without causing a ripple effect of delays. It can also let two staff members be Chairside for the initial cannulation. The cannulator can focus on the cannulation. The second staff member can focus on supporting the patient while also being available for immediate assistance for troubleshooting any cannulation difficulties. The concept can also facilitate the use of point-of-care ultrasound (POCUS).

HD patients are typically dialyzed in a reclining chair. The position of the cannulator for the actual needle insertion can also impact the cannulation success. Standing is a typical positioning of the staff member for cannulation procedure, and this position can generate a downward force from the cannulator's body to the AVF needle. The downward force can lead to the sharp needle bevel cutting the vessel and then going into the back wall leading to a backwall infiltration. If the cannulator sits on a stool to be level with the vascular access, the downward pressure is easier to control. It also places the staff member at eye level to the patient and can reduce the fear/anxiety of the patient (Table 16.3).

Cannulation-Induced Needle Fear or Phobia

Cannulation of patients' HD vascular access can trigger needle fear or needle phobia. The prevalence of needle fear in dialysis patients ranges from 25% to 55%. Needle phobia has also been cited by 47% of in-center HD patients as a barrier to self-care. A typical in-center HD patient undergoes 312 needle cannulations per year. Home HD therapies often have an even higher number of treatments per week, with a higher resultant number of cannulations per year (Table 16.4).

The 2020 ICD-10-CM Diagnosis Code F40.231 defines needle fear or needle phobia as the fear of injections and transfusions. The ICD-10-CM F40 diagnosis code defines phobic anxiety disorders as an irrational fear of something that poses little to no actual physical harm. Exposure to the trigger of the phobia can lead to physical symptoms including panic and fear, rapid heartbeat or palpitations, shortness of breath, trembling or shaking, strong desire to get away from the trigger, dizziness or unsteadiness, nausea, and sweating.

Needle fear prevalence rates vary by age grouping (refer to Table 16.5). McLenon and Rogers reported a difference

TABLE 16.2 **Combined Physical Exam/Monitoring Check**

One Minute Check (Novice/Expert), Vascular Access 2018 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS) and 2019 KDOQI Vascular Access Guidelines

Exam or Check Step	Fistula Normal Green Light	Graft Normal Green Light	Flow-Related Dysfunction or Poor Maturation (Abnormal) Red Light	Infection, Steal Syndrome, or Aneurysm/Pseudo-aneurysm (Abnormal) Red Light
Look	The skin over the access is all one color and looks like the skin around it. Well-developed main venous outflow, no irregular/dilated areas or aneurysm formations, adequate areas of straight vein that can be used for two-needle, rope ladder cannulation.	Pulse does not become more forceful or "strong and bounding." Uniform-sized graft in a loop or straight configuration. No irregular areas or aneurysm or seroma formations with organized site rotation used for cannulation.	Presence of swelling. Rich collateral veins. AVF with poor maturation—multiple venous outflow veins (accessory veins), poorly defined cannulation areas. AVF: Stenosis can occur in artery or any venous outflow vein. Look for a narrowing of the outflow vein, abnormal pulsations, or aneurysm formation. AVF or AVG: Dilated neck veins or surface collateral veins in the arm or neck above the vascular access.	There is redness, swelling, or drainage. There are skin bulges with shiny, bleeding, or peeling skin. Ischemic fingers: Fingertip wounds like paronychia Aneurysms: Nonhealing crust over the puncture site. Infection: Redness, swelling, induration, drainage, or pus Steal syndrome: Extremity/hand discoloration, skin ulceration due to poor arterial blood flow to the hand. Check nail beds, fingers, and hand for unusual skin changes Aneurysm: Abnormal areas of dilatation with overlying skin thinning
Listen	Bruit—the hum or buzz should sound like a "whoosh," or for some may sound like a drumbeat. The sound should be the same along the access. Low-pitch continuous diastolic and systolic.	Bruit—the hum or buzz should sound like a "whoosh," or for some may sound like a drumbeat. The sound should be the same along the access. Low-pitch continuous diastolic and systolic.	There is no sound, decreased sound, or a change in sound. Sound is different from what a normal bruit should sound like. Strictures can be palpated and the intensity and character of the bruits can suggest the location of stenoses. (AVF) A local intensification of bruit over the graft or the venous anastomosis compared with the adjacent segment suggests a stricture or stenosis. (AVG) High-pitch discontinuous systolic only.	AVF may have a very strong bruit.

Continued

TABLE 16.2 **Combined Physical Exam/Monitoring Check—cont'd**

Exam or Check Step	Fistula Normal Green Light	Graft Normal Green Light	Flow-Related Dysfunction or Poor Maturation (Abnormal) Red Light	Infection, Steal Syndrome, or Aneurysm/Pseudo-aneurysm (Abnormal) Red Light
Feel	Thrill: a vibration or buzz in the full length of the access. Pulse: slight beating like a heartbeat. Fingers placed lightly on the access should move slightly. Thrill at the arterial anastomosis and throughout the entire outflow vein that is easy to compress	Thrill: a vibration or buzz in the full length of the access. Pulse: slight beating like a heartbeat. Fingers placed lightly on the access should move slightly. Thrill strongest at the arterial anastomosis but should be felt over entire graft and be easy to compress.	Pulsatile: The beat is stronger than a normal pulse. Fingers placed lightly on the access will rise and fall with each beat. Rich collateral veins A strong pulse and weak thrill in the vein central to the anastomosis indicates a draining vein stenosis. A strong pulse and weak thrill in the vein central to the anastomosis indicates a draining vein stenosis. AVF: Pulse at the site of a stenotic lesion—may be water-hammer in quality and feel. AVG: Thrill and/or pulse strong at the site of stenotic lesion pulse has a water-hammer feel. An AVG with a low intra-access blood flow feels mushy. Local area of the graft that feels mushy or irregular in shape can be a site of aneurysm formation.	Ischemic fingers Aneurysms Infection: Warm or painful to touch, swelling Steal syndrome: Feel bilateral limbs (hands and fingers) and compare for the access limb to be the same as the nonaccess limb. Compare temperature, grip strength, and range of motion and any complaints of changes in sensation or pain. If the access limb has any major differences than the nonaccess limb, consider steal syndrome
Arm elevation test	Upper arm AVF: Arm elevation. The AVF outflow vein partially collapses when the arm is raised above the level of the heart. It may feel "flabby" when palpated. Lower arm AVF: The AVF outflow vein collapses when arm is raised above the level of the heart. Vessel collapses when the arm is elevated above head Normal		Upper arm AVF: The AVF outflow vein does not partially collapse or become "flabby" after being raised above the level of the heart. This finding should be reported to an expert clinician. Lower arm AVF: The AVF outflow vein does not collapse after being raised above the level of the heart. This finding should be reported to an expert clinician. A fistula that does not at least partially collapse with arm elevation is likely to have an outflow stenosis. Vessel collapses when arm is elevated above head.	

Augmentation test	Pulse should be “strong and bounding” and may cause your finger to rise and fall with each beat	Pulse does not become more forceful or “strong and bounding”.
Dialysis observations:		
New difficulty with cannulation when previously not a problem.		
Aspiration of clots.		
Inability to achieve the target dialysis blood flow.		
Prolonged bleeding beyond usual for that patient from the needle puncture sites for three consecutive dialysis sessions.		
Unexplained (> 0.2 units) decrease in the delivered dialysis dose (Kt/V) on a constant dialysis prescription without prolongation of dialysis duration.		

AVF, Arteriovenous fistula; *AVG*, arteriovenous graft.

TABLE 16.3 Cannulation-Related Practice Guidelines

Guideline Reference	Guideline Statement
2019 KDOQI Vascular Access Guideline 11.6	KDOQI considers it reasonable to use skilled cannulators with established high rates of cannulation success to perform initial AV access cannulations on patients to help avoid primary infiltration injury of the AV access. (Expert Opinion)
2019 KDOQI Vascular Access Guideline 11.7	KDOQI considers it reasonable to have structured training and supervision of dialysis technicians and nurses before and during their initial cannulation attempts, and regular training updates to maintain cannulation competency. (Expert Opinion)
2019 KDOQI Vascular Access Guideline 11.8	KDOQI considers it reasonable to support and educate eligible patients on self-cannulation of their AV access. (AVF or AVG). (Expert Opinion)
2018 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS) 6.3.2.2.	Ultrasound-assisted cannulation. The statement supports ultrasound-assisted cannulation to reduce cannulation infiltration related complications. ESVS states randomized controlled trials of ultrasound-guided cannulation versus unassisted cannulation to determine benefit is required. The statement also supports ongoing education and training of the dialysis facility staff on cannulation techniques.

AV, Arteriovenous; *AVF*, arteriovenous fistula; *AVG*, arteriovenous graft; *KDOQI*, Kidney Disease Outcomes Quality Initiative.

TABLE 16.4 Number of Cannulations per Year Based on Dialysis Frequency

Treatment Frequency	Needles per Session	Weeks in a Year	Total Number of Cannulations per Year
3	2	52	312
4	2	52	416
5	2	52	520
6	2	52	624
7	2	52	728

Additional cannulations due to needle insertion complications such as infiltration are not included in the table.

TABLE 16.5 Prevalence Rates of Needle Phobia by Age Grouping

Age Grouping	Prevalence Rates of Needle Phobia
Children	50%–100% decreases with age
Adolescents	20%–50%
Young adults	20%–30%
Adults	16%
Elderly	<5%

based on sex as females report a higher prevalence of needle fear compared with men. The prevalence of needle fear and phobia in the pediatric HD population ranges from 50% to 100%. Care partners of adult home HD patients or caregivers of pediatric HD patients may also have a fear of needles. Health care workers are not immune to needle fear issues, as 1 in 6 long-term care facilities and 1 in 13 hospital workers avoid annual influenza vaccinations due to fear of needles.

The high prevalence of needle phobia in the HD population must be addressed by the dialysis care team. The individualized patient plan of care should include measures to reduce the fear and the triggers of related phobia symptoms. The most common intervention is the use of local topical anesthesia. Table 16.6 includes infection control considerations for each agent. The use of any agent should be individualized for each patient based on the cannulation method (staff cannulation, self-cannulation, rope ladder, or buttonhole). The therapeutic effectiveness should be documented and reviewed as part of the ESKD Life Plan under vascular access type. Should the cannulation method require modification, the pain control measures should be reviewed and updated as needed. Anesthesia agents may require a physician's prescription, and the dispensing process varies by local laws.

Cannulation Technique Customization

The cannulation technique should be customized to the specific conduit (vessel, synthetic, or biological material). The manufacturers of the various vascular graft materials can provide recommended best practices for cannulation. Variables include needle gauge and length, utilization of a tourniquet, arterial and venous needle placements, advancement to two-needle cannulation, the needle angle of entry, and method of needle advancement. Refer to Table 16.7.

General Initial Cannulation Suggestions

The KDOQI 2019 Vascular Access Guidelines have removed previous KDOQI 2006 Vascular Access Guidelines detailed procedure steps for initial AVF or AVG cannulation (Table 16.8). The 2019 update recommends the initial

TABLE 16.6 Cannulation Pain Control Measures

Measure to Reduce Needle Fear/ Pain	Description of Use	Infection Control Considerations	Other Considerations
Local topical anesthesia such as a lidocaine cream. Impact on needle phobia: High. Peds: Can be utilized with pediatric patients. Check drug instructions for use for a minimum age or weight requirements	Follow instructions for use for contact time with the skin to achieve adequate effect of anesthesia on the skin over the needle cannulation sites. Typically requires application 1 hour prior to the cannulation. Can be applied at home and cover with plastic wrap. Note the maximum recommended duration of exposure is usually 4 hours—check drug instructions for use. Each patient is given a prescription for their drug and applies the drug at home and not in the hemodialysis environment.	The skin prep steps: Washing the cream off the cannulation sites with soap and water at the skin prior to sitting into the dialysis chair. If the patient is unable to wash, the staff should use skin wipes to remove and cleanse the skin. If utilized with buttonhole cannulation, the cream must be cleansed from the skin prior to the buttonhole scab removal procedure. Unit-specific skin prep for routine cannulation.	The amount of the topical anesthesia should follow the drug instructions for use to ensure the dosage is below the maximum application area. Check instructions for use for cm^2 as area coverage. If plastic wrap is applied to cover the cream, the wrap should not impede blood flow in the AV access. Needle site rotation must be clearly determined to ensure the patient applies the topical anesthesia in various locations allowing proper rope ladder and avoids area puncture.
Intradermal lidocaine. Impact on needle phobia: Poor as the intradermal injection requires a needle and the lidocaine causes burning sensation when injected.	Injected from a syringe via a small-gauge needle.	Should use a separate syringe/needle for intradermal injection. Skin prep of washing with soap/water as well as the initial skin prep prior to the intradermal injection procedure. The needle should be a safety needle to prevent accidental needle stick to the cannulator.	
Place the patient in the Trendelenburg position for cannulation. Impact on needle phobia: High in patients with physical manifestations of needle phobia.*	Elevation of lower extremities in the recumbent position with applied muscle tension augments the central venous reservoir, increases stroke volume, and helps maintain cerebral perfusion.		Chair/dialysis machine positioning to allow the staff member to reach the lower or upper arm cannulation sites with the patient in the Trendelenburg chair position.
Ethyl chloride topical anesthetic skin Refrigerant Impact on needle phobia: Moderate as the numbing effect is on the skin surface, not deeper tissue	Spray the cannulation for few seconds—check drug instructions for use for time or until the skin color begins turning white, whichever comes first.	The drug is available in both a can and a bottle. Infection control practices require any item that enters the direct patient station to be surface disinfected or single use only. This can be a barrier to use in the in-center hemodialysis facility.	
Alternative measures: Topical application of lavender† Impact on needle phobia: Limited studies to determine	Topical application of 100% lavender essential oil decreases moderate intensities of pain during needle insertion.	Oils are over-the-counter products and thus are not tested or controlled for proper concentration or any contaminants. The oil container must be limited to a single patient to prevent cross-contamination. Proper skin disinfection should occur after the application of the oil to prevent cross-contamination of the needle site.	

AV, Arteriovenous.

* Hamilton JG. Needle phobia: a neglected diagnosis. *J Fam Pract*. 1995;41(2):169-175.

† Ghods AA, Abforosh NH, Ghorbani R, Asgari MR. The effect of topical application of lavender essential oil on the intensity of pain caused by the insertion of dialysis needles in hemodialysis patients: a randomized clinical trial. *Complement Ther Med*. 2015;23(3):325-330.

TABLE 16.7 Conduit Cannulation Recourses

Product Name	Website for Cannulation Recommendations
Gore PTFE— standard	https://www.goremedical.com/products/vg
Gore Acuseal	https://www.goremedical.com/products/acusealvg
Getinge Flixene	https://www.getinge.com/int/products/hospital/vascular-and-cardiothoracic-surgery-solutions/eptfe-grafts/
Artegraft Collagen Vascular Graft	https.www.lemaitre.com/productss
Merit Medical HeRO	https://www.merit.com/peripheral-intervention/access/renal-therapies-accessories/merit-hero-graft/
BD Bard WavelinQ EndoAVF system	https://www.crbard.com/Peripheral-Vascular/en-US/Products/WavelinQ-EndoAVF-system
The Ellipsys Vascular Access System	https://www.medtronic.com/us-en/healthcare-professionals/products/cardiovascular/arteriovenous-fistula-creation/ellipsys-vascular-access-system.html

PTFE, Polytetrafluoroethylene.

TABLE 16.8 Initial Cannulation Guideline References

Guideline Reference	Guideline Statement
KDOQI 2019 Vascular Access Guideline 11.1	KDOQI considers it reasonable to assess or check the vascular access and surrounding area by physical exam prior to every cannulation (if AV access) or connection (if CVC) for potential complications. (Expert Opinion)
KDOQI 2019 Vascular Access Guideline 12.1	KDOQI considers the following therapeutic interventions for cannulation injury reasonable to follow: • Any size infiltration: apply ice for a minimum of 10 minutes and refrain from maximizing the blood pump speed. (Expert Opinion) • If the infiltration is moderate, the needle should be withdrawn and manual pressure held over the infiltration site. (Expert Opinion) • If the infiltration is significantly large, in addition to the above, a decision on the necessity for dialysis that day is required—if dialysis is required, a site proximal to the infiltration injury should be cannulated; if this is not possible, reattempt at the area of the injury should not proceed until the manual pressure and ice is applied for 30 minutes. (Expert Opinion) • If a hematoma develops, close assessment of the site, the AV access, and the adjacent extremity should be made, including measurement of swelling, assessment of the presence of flow in the AV access both proximal and distal to the hematoma, and circulation to the associated extremity. (Expert Opinion)
KDOQI 2019 Vascular Access Guideline 11.6	KDOQI considers it reasonable to use skilled cannulators with established high rates of cannulation success to perform initial AV access cannulations on patients to help avoid primary infiltration injury of the AV access. (Expert Opinion)
2018 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS) 6.3	Guideline text includes a description of cannulation steps and methods— Recommendation 42: In patients with a short cannulation segment the use of the buttonhole technique should be considered over other techniques (note only in AVF) Recommendation 43: The rope ladder technique should be used for cannulation of arteriovenous grafts.

AV, Arteriovenous; *CVC*, central venous catheter; *AVF*, arteriovenous fistula; *KDOQI*, Kidney Disease Outcomes Quality Initiative.

cannulation be customized to meet the requirements of the ESKD Life Plan regarding modality selection and vascular access. The ESKD Life Plan example is a patient selecting nocturnal home HD that will utilize self-cannulation of their AVF. The customization is the use of smaller-gauge needles as a blood flow rate of less than 300 mL/min is typically used for nocturnal home HD. The cannulation method is then customized to the buttonhole or rope ladder cannulation method. The buttonhole cannulation method should take into consideration the unique patient clinical conditions, including any conditions that might exclude the use of buttonhole cannulation such as a mechanical heart valve, poor skin integrity, previous vascular access infections, or osteomyelitis, and active wound infection. Other patient factors such as needle fear/phobia, hand dexterity, cannulation zone length and placement, eyesight, and ability to maintain proper infection control measures should also be considered when selecting the cannulation method, as well as a backup plan should cannulation issues arise in the future.

The initial AVF cannulation policy and procedures vary by the dialysis provider. The general elements are described here:

- Use of the arterial metal AVF needle cannulation as the draw for the arterial bloodline connection and the HD catheter as the venous return (either lumen connected to the venous bloodline). This is commonly referred to as "one and one" by the dialysis staff. The rationale for this policy/procedure is to reduce the risk of infiltration. If the arterial needle site should infiltrate, the severity of the infiltration will be limited to bleeding from the needle movement outside the vessel. The arterial needle is under negative pressure of the blood pump trying to pull blood into the extracorporeal circuit.
- The venous return via the venous needle is under positive pressure. The blood pump forces the blood from the extracorporeal circuit to the venous needle. Should a venous needle infiltration occur, the blood is pushed into the infiltration area until the venous pressure rises to the alarm limit level.
- Use of a wet AVF metal needle for the cannulation. The procedure utilizes a normal saline solution–filled 10-cc syringe to be attached to the AVF needle. Right before the needle is used for cannulation, the needle tubing and needle are primed with normal saline solution to purge all air. The syringe remains attached as the AVF needle is inserted into the AVF vessel. The blood flashback can be muted due to the saline, and thus the cannulator can pull back slightly on the 10-cc syringe plunger to check for a good blood return. Once the needle is checked for the blood return, the saline can be carefully infused to check for any indications of infiltration, such as the patient reporting an increase in pain at the cannulation site, increased resistance to the saline infusion, and/or visual evidence of a fluid bleb or infiltration.
- Delay the administration of the heparin bolus (or other anticoagulants) until the AVF is successfully cannulated and the needle is checked with the saline flush to rule out an infiltration. The heparin can then be administered via the HD catheter lumen or venous needle. The delayed heparin administration allows the safe removal of the infiltrated needle without the effects of prolonged bleeding from the heparin. The post-catheter heparin lock (or other anticoagulants locks) may also be held until the AVF needle is removed and hemostasis is achieved.
- The KDOQI 2019 Vascular Access Guidelines Guideline 12 addresses AV access cannulation complications. Refer to Table 16.8. Follow unit-specific policy and procedure for the treatment of an infiltration. If the policy includes the application of ice, heat, or any topical agents (e.g., Arnica homeopathic herb in cream formulation) to reduce the infiltration, hematoma, or bruising, then simple-to-follow written instructions should be provided to the patient and caregiver.
- Needle gauge and blood flow rate advancement protocols vary by provider. The needle gauge advancement typically starts with the smallest needle gauge that supports the initial blood flow rate. The theory is that the smaller needle will create a smaller-diameter vessel entry hole. Should the needle infiltrate into the side or backwall, the infiltration is also limited to the smaller needle puncture hole in the vessel. After a limited number of cannulations, such as three, the needle gauge is increased to the next larger gauge. The blood flow rate is also increased to match the range of the needle gauge (Table 16.9).
- The timing of removal of the HD CVC may also be included in the initial cannulation protocol. The protocols typically have a target needle gauge and corresponding blood flow rate that is achieved with consecutively successful cannulations before the catheter is removed. Some of the protocols include scheduling the catheter removal appointment in advance and then adjusting the appointment date as needed. Careful communication among the dialysis care team, patient, and surgeon or interventionalist must occur to ensure the proper catheter removal timing.
- New AVF as the sole access requires both arterial and venous needle cannulation. The arterial needle is typically cannulated first. This is done in case a complication with infiltration occurs. The needle can be pulled and the site held to achieve hemostasis prior to any attempts to cannulate again in a site proximal of the infiltration. If the infiltration is severe and successful cannulation

TABLE 16.9 Needle Gauge to Correlate with the Blood Flow Range

Needle Gauge	Blood Flow Rate
17	<300 mL/min
16	300–350 mL/min
15	350–450 mL/min
14	>450–mL/min

cannot be achieved with a three-needle attempt, the need for dialysis should be assessed as stated in the KDOQI 2019 Vascular Access Guideline 12.1, as referred to in Table 16.8. The patient may require an HD catheter so the AVF can rest and resolve the hematoma.

- Endovascular AVF initial cannulation policy and procedure may include a blend of the previous elements. The cannulation zones can vary based on the specific device used to create the anastomosis. A policy and procedure should be created and fully implemented prior to the need for the first endo-AVF cannulation. Refer to Table 16.7.
- The initial standard AVG material cannulation policy and procedures vary by the graft material and the dialysis provider. The general elements can include cannulation with two needles of the required needle gauge to achieve the targeted blood flow rate prescribed to achieve adequate dialysis. The rationale is that the standard AV graft conduit is of a set inner diameter and only requires healing of ingrown tissue and resolution of localized edema from surgery. The conduit puncture will typically withstand the needle gauge without infiltration. Infiltrations occur when the AVG is too deep, and the standard 1-in AVF needle is not long enough to puncture the graft and be properly advanced into the blood pathway. The AVG can also infiltrate from improper needle advancement. If the angle of entry is not leveled out when advancing the needle, the backwall can be punctured, creating a backwall infiltration. The backwall infiltration is very difficult to control as direct pressure to the backwall is challenging to achieve without occluding the access at the injury site.
  The initial early cannulation AVG material cannulation policy and procedures vary by the graft material and the dialysis provider. The use of a smaller needle gauge and lower blood flow rates might be recommended to provide less turbulence at the venous anastomosis and reduce the risk of rupture of the venous anastomosis. This also applies to any unique graft materials or configuration, such as a biological graft or HeRO AVG or AVF. Refer to Table 16.7 for resources for the specific conduit.
- Use of fistula cannula needle (fistula catheter needle or a plastic needle) can be utilized in the new AVF cannulation policy and procedure, including the cannulation of endovascular AVF. Please consult with the device manufacturer for suggested cannulation policy and procedure elements. A policy and procedure should be created and fully implemented prior to the need for the utilization of the fistula cannula needle (refer to Table 16.10).

Cannulation Methods

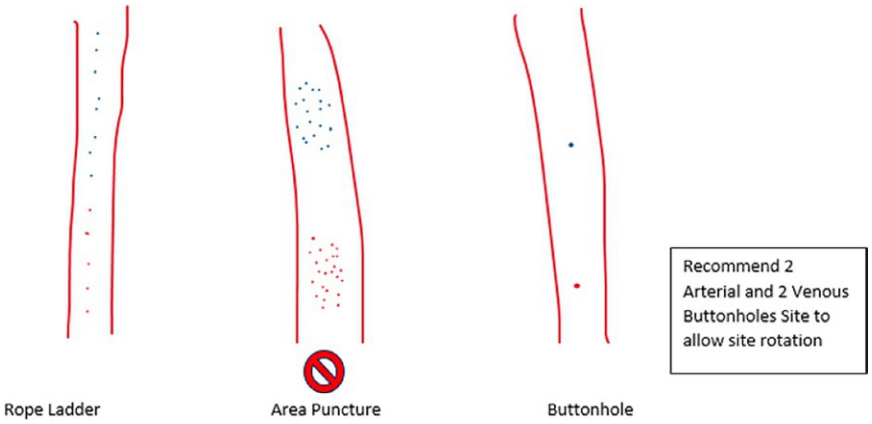
The actual step of needle insertion in the overall cannulation procedure is the art element. The written policy and procedure should be based on the science of cannulation. The art of cannulation is similar to painting. A painter grips the paintbrush and applies different degree of pressure to the brush as part of the application of the paint to the canvas. A skilled painter can adjust the degree of pressure being applied to the brush as well as feeling the resistance of the paint moving on the canvas. The same concept applies to cannulation. The cannulator must have fine motor skills that allow them to sense the pressure applied on to the AVF needle as the needle encounters different resistance of the skin, subcutaneous tissue, and vessel wall. The expert cannulator is keenly able to quickly process the pressure resistance as the needle penetrates the various tissues and quickly adjust the pressure. A novice cannulator frequently holds the wings of the AVF needle with an excessive grip and thus cannot sense the subtle changes in resistance. The excessive grip can cause the novice cannulator to enter the vessel and not slow the needle entry rate and thus penetrate the backwall of the AVF or AVG, resulting in a backwall infiltration. When training new staff, this step in the cannulation process is challenging to evaluate with the current fake arms available for training. A cannulation simulator model can potentially capture the art elements of cannulation and provide feedback to the cannulator on pressure, angle, and needle advancement technique.

Rope ladder is the preferred method of AVF and AVG cannulation. Buttonhole cannulation may be the appropriate method based on the individualized patient ESKD Life Plan and current vascular access. Area puncture is not an acceptable method of cannulation but is the most commonly utilized in actual practice (Fig. 16.1).

TABLE 16.10 Plastic AVF Cannula or Needle Resources

Product Name	Lengths	Gauges	Special Considerations for Use
Medtronic Argyle Safety Fistula Cannula with Antireflux Valve	25 to 38 mm 0.98 to 1.50 in	17, 16, and 15	Use for first-ever cannulation for AVF, endovascular created fistulae and for home hemodialysis to reduce infiltration with access movement.
Safetouch AVF Catheter Needle https://www.nipro-group.com/en-en/products/safetouchtm-avf-catheter-needle	20 to 38 mm 0.70 to 1.50 in	17, 16, 15, and 14	

AVF, Arteriovenous fistula; *FDA*, Food and Drug Administration.



Cannulation Method	Vascular Access Type	Description of Arterial/ Venous Needle Locations	Recommendations VA Guidelines Including KDOQI 2019 and ESVS 2018
Rope ladder	AV fistula—surgical or endo AV graft (synthetic or biological)	Cannulation site is moved up and down the cannulation zone to allow full site rotation.	Considered the best practice for routine AV fistula of AV graft cannulation method. Supported by ESVS guideline 6.3.2.3 and KDOQI guideline 11.2.
Area puncture	AV fistula—surgical or endo AV graft (synthetic or biological)	Limited segment of the cannulation zone is used for repeated cannulation.	Not recommended as a cannulation method, however, is the most common form of cannulation in actual practice. Supported by ESVS guideline 6.3.2.4. and KDOQI guideline 11.2.
Buttonhole	AV fistula—surgical or endo	Exact same cannulation site is utilized to create a tissue tunnel track.	Limited cannulation zones. Supported by Guidelines: ESVS Recommendation 42 11.3 KDOQI considers it reasonable to limit AV access buttonhole cannulation only to special circumstances given the associated increased risks of infection and related adverse consequences. Self-cannulation (in-center or home dialysis) Can mix buttonhole and rope ladder cannulation method if arterial or venous cannulation zone has limited length/depth and requires a buttonhole cannulation method. Rope ladder cannulation can also be utilized away from the buttonhole sites due to inability to use the buttonhole sites (self-cannulator unable to cannulate or to successfully utilize a buttonhole site or lack of buttonhole blunt needles). Buttonhole should not be used in synthetic PTFE grafts. Supported by Guideline 1.4 KDOQI and Recommendation 43 ESVS. 11.5 KDOQI suggests that when select buttonhole cannulation is performed, the use of buttonhole cannulation devices to facilitate cannulation should be at the discretion and expertise of the cannulator.

AV, Arteriovenous; *ESVS*, European Society for Vascular Surgery; *KDOQI*, Kidney Disease Outcomes Quality Initiative; *PTFE*, polytetrafluoroethylene.

• **Fig. 16.1** Cannulation Methods.

General Cannulation Policy and Procedure Steps

The access site and surrounding skin area should be washed at a clean sink with soap and water by patients prior to entering their HD station.

Any patient unable to wash their access site should have the access site and surrounding skin area cleaned with a general skin disinfectant wipe.

The One Minute Check using an aseptic technique, including cleaning the stethoscope, is performed before the cannulation steps. The "look, listen, and feel" check should also be utilized to identify the cannulation zones and previous cannulation patterns.

The cannulation method should be identified as part of the ESKD Life Plan under the vascular access: rope ladder, buttonhole, or a mixture of buttonhole and rope ladder in different cannulation zones. The method should correspond to the vascular access type (AVF, endovascular AVF, AVG, biologic graft, or HeRO) and manufacturer's recommendations.

Infection control measures to ensure aseptic technique should be detailed and followed per the facility-specific cannulation policy and procedure. Adherence to the policy and procedure should be routinely monitored as part of the facility-specific continuous quality improvement (CQI) process (https://www.asn-online.org/ntds/resources/).

Patients should be fully educated on the infection control policy and procedure. The patient has the right and should be empowered to identify if any breaks in proper infection control measures occur and can request correction of the break before the cannulation proceeds. For example, the cannulator may fail to change gloves after touching contamination of a dirty surface such as the biohazard bin and then picking up the AVF needle for cannulation. Patient empowerment is critical and should occur without the patient fearing retribution by the facility staff.

The skin over and surrounding the cannulation site disinfection steps and contact time of the disinfecting agent should follow the manufacturer's instructions for use.

The policy and procedure should include alternative disinfecting agents to allow individualization should allergic reactions of skin breakdown occur. Special disinfecting agents should also be included in the ESKD Life Plan as part of the vascular access. They may require a physician order to ensure proper use for the individual patient. The allergy list for the patient should be updated to include the specific disinfection agent that may have triggered an allergic reaction and detail the reaction type and severity.

The needle or cannula type, gauge, and length should be included in the physician order and individualized according to the ESKD Life Plan under the vascular access.

Each specific vascular access type and a unique conduit require a specific initial and routine cannulation policy and procedure. Algorithms can be used to detail the advancement of the cannulation process, such as needle gauge and blood flow rate advancement.

The use of dry or wet needles for cannulation can also be detailed in the cannulation algorithm as part of the policy and procedure.

Venous needle insertion direction should always be toward the venous return back to the heart.

The arterial needle insertion should be individualized based on the cannulation zone length, depth, and flow direction. An endovascular AVF can have split flow; thus, the arterial needle should be placed into the vessel with a higher flow rate. The needle direction can be retrograde or antegrade.

The use of a tourniquet or manual pressure to compress the venous outflow and dilate the cannulation zone should correspond to the vascular access type (AVF, endovascular AVF, AVG, biologic graft, or HeRO) and manufacturer's recommendations.

Needle securement varies with the facility-specific policy and procedure. The method should also be adjusted to correspond with the ESKD Life Plan as part of the vascular access. It may require a physician order to ensure that the proper method is selected for the individual patient (self-cannulation or home HD). The goal of preventing accidental needle dislodgement is the overarching goal for all securement methods. If any accidental needle dislodgement occurs, securement methods should be evaluated for proper adherence to the written policy and procedure and effectiveness.

Detection of disconnection or dislodgement of the venous needle is an essential element of monitoring the HD treatment. The basic method is that the access sites remain visible at all times after the insertion of the needle and until after the removal of the needle and hemostasis has been achieved. The access site should be fully exposed and removed from covering with clothing, blankets, or other objects (https://www.homedialysis.org/life-at-home/helpful-products/clothing). Technology-assisted needle dislodgement includes standalone products such as Redsense Medical devices (https://redsensemedical.com/). Some HD machine manufacturers have also integrated venous dislodgment detectors into the functionality of HD machines (https://www.freseniusmedicalcare.com/en/healthcare-professionals/hemodialysis/machines/5008-cordiax-5008s-cordiax/).

Needle removal is also a key element of cannulation. Needle removal may be part of the policy and procedure for HD treatment termination and may vary by access type.

Key needle removal elements for all access types include the following: Complete withdrawal of the needle from the vessel and skin before the application of direct pressure to avoid accidental cutting of the vessel or skin from the needle cutting surface on the needle bevel. Direct pressure with a two-finger hold over the needle entry to the vessel location and the skin exit site is recommended. The pressure should be maintained without "peeking" to see if the bleeding has stopped for a set amount of time specific to the patient's access type and cannulation method. Typically, AVF cannulation sites reach hemostasis with less direct pressure time than standard polytetrafluoroethylene (PTFE) graft

material. The goal is to hold enough direct pressure to control bleeding and allow for the formation of a localized clot at the cannulation site without excessive pressure that might occlude the vascular access. The presence of thrill in the access beyond the pressure site should be checked to ensure excessive pressure is not be applied that could cause vessel occlusion.

The arterial and venous needle removal sequence should also be included in the policy and procedure. The removal of the arterial needle first may facilitate the utilization of the venous needle for saline infusion post HD should it be necessary for intervention for post-dialysis hypotension.

The removal of one needle at a time can allow for better control of manual pressure application over the needle site. Manual pressure can be applied by the dialysis staff member, patient, or care partner. Proper pressure application can prevent the use of excessive pressure that can impede the access blood flow that can cascade into a thrombotic event. Holding one needle site at a time may decrease the total time of post needle manual application of pressure.

Patients should be trained to assist with manual pressure application over the needle site. Proper infection control measures such as the use of a glove on the hand holding the site should be routinely utilized.

The facility policy and procedure should outline the patient selection criteria and implantation of the use of any external clamps to achieve hemostasis post needle removal. The use of clamps in frail, elderly, or confused patients poses the risk of blood loss if the clamp becomes dislodged or bleeds around the clamp pressure point. Thus, if the use of clamps is determined to be necessary, the user must be witnessed by a staff member to ensure that any bleeding around the clamp is detected and corrected to prevent blood loss.

Once hemostasis is achieved, the needle site should be covered with a clean dressing and tape or an adhesive bandage. The tape should not be applied around the full circumference of the arm or leg to prevent excessive pressure and impediment in the flow within the vascular access.

Patients and care providers (such as nursing homes) need written/visual instructions detailing the post needle site dressing/bandage care and time when the cover can be safely removed. The instructions should also include detailed instructions on how to respond to rebleeding that might occur. Fatal vascular access hemorrhage occurs most commonly outside the dialysis facility in the patient's residence, and it can be witnessed or unwitnessed, and death may occur before emergency responders can arrive. The patient, family members, transport personnel, and caregivers (including skilled care locations) should be provided simple instructions on the emergency response to bleeding from an HD vascular access. Vascular access bleeding control teaching tools are available from the British Renal Society (https://britishrenal.org/aboutus/special-interest-groups/).

The cannulation policy and procedure need to also include steps to respond to cannulation complications such as infiltration. The KDOQI Guidelines details the recommended response to infiltration: 12.1 "KDOQI considers the following therapeutic interventions for cannulation injury reasonable to follow: Any size infiltration: apply ice for a minimum of 10 minutes and refrain from maximizing the blood pump speed. If the infiltration is moderate, the needle should be withdrawn and manual pressure held over the infiltration site. If the infiltration is significantly large, in addition to the above, a decision on the necessity for dialysis that day is required—if dialysis is required, a site proximal to the infiltration injury should be cannulated; if this is not possible, reattempt at the area of injury should not proceed until manual pressure and ice is applied for 30 minutes. If a hematoma develops, close assessment of the site, the AV access, and the adjacent extremity should be made, including measurement of swelling, assessment of the presence of flow in the AV access both proximal and distal to the hematoma, and circulation to the associated extremity."

General Buttonhole Cannulation Policy and Procedure Steps

Infection control elements of the facility-specific policy and procedures need to be detailed, implemented, and audited to reduce the risk of infection from the buttonhole cannulation method.

The access site and surrounding skin area should be washed at a clean sink with soap and water by the patient before entering their HD station. The access wash step can help to soften the scab that covers the previous treatment buttonhole scab and allow nontraumatic scab removal.

The previous treatment buttonhole site scab should be gently removed to prevent bleeding in the tissue around the scab edges. If bleeding occurs, the skin is no longer intact, and a sharp needle for rope ladder cannulation away from the buttonhole site should be considered.

The previous treatment buttonhole site scab can be removed with the skin disinfection application.

The scab must not be "picked off" with the needle bevel or tweezers, as this is a known break in infection control that can lead to an infection. Buttonhole needles are available with a dull scab removing device integrated into the needle package design. The device should be utilized to remove the scab as per the manufacturer's instructions for use.

Sharp needles should be utilized to create the buttonhole needle tracks only. The transition from sharp to blunt buttonhole needles should be individualized for each patient, but general guidelines for the number of cannulations should be included in the policy and procedure. Once the buttonhole is established, the routine use of a sharp needle is contraindicated.

The development of two arterial and two venous buttonhole sites should be established if feasible. If only one cannulation site utilizes buttonhole, then two sites should be created in the appropriate cannulation zone.

Should the patient require HD and the buttonhole needles or a trained cannulator is not available, the rope ladder with sharp needles should be utilized to cannulate far enough away from the buttonhole sites to prevent the entry of the needle into the buttonhole tunnel track.

The buttonhole tunnel track and the AVF vessel opening can move as the tissue surrounding the tunnel track moves due to fluid-gain related edema, weight gain, a difference in the limb positioning, or use of a different buttonhole needle brand. If the buttonhole tunnel tracks are created by the dialysis personnel, and then the patient takes over self-cannulation, the misalignment can occur. The misalignment can occur due to the different limb positioning or difference in the needle angle of approach due to hand positioning for cannulation.

Post needle removal process, obtainment of hemostasis is the same as the general cannulation. A difference can be the time required to hold pressure over the buttonhole sites as buttonhole sites can have shorted post-needle-removal bleeding time. This should be individualized for each patient.

Arterial needle insertion direction can be retrograde or antegrade.

Self-cannulation

Self-cannulation is often required for home HD or self-care HD. The utilization of self-cannulation for in-center HD patients is not a common practice. A typical root cause for the low use of self-cannulation for in-center patients is frequently related to the dialysis staff workflow and time utilization. The time for the cannulation procedure is included in the time allotment for the overall dialysis initiation procedure. A patient learning self-cannulation will require extended time allotment for the cannulation portion of the dialysis initiation procedure. The need to adjust the staff member assignments can create issues with overall staffing and timing of other patients' dialysis initiation. Increasing the percentage of patients utilizing self-cannulation requires creative staff and patient scheduling and workflows. Solutions may include the involvement of the home HD training staff, nurse educator, or training preceptor to assist with the cannulation training.

The training curriculum should be based on the facility cannulation policy and procedures with any adaptations required for a self-cannulator. The training plan should be customized to the individual patient and should be competency based. The medical record should have full documentation of the training and the achievement of competency by the patient for self-cannulation.

The transitional dialysis care model is increasingly being adopted. Self-cannulation in-center can be the first step toward the patient moving into self-care or home HD. If home HD is the targeted modality, with buttonhole as the ideal cannulation method, the patient or care partner should establish the buttonhole site whenever possible. The cannulation competency can be part of the transitional dialysis care model.

Cannulation Process of Care Utilizing POCUS and Cannulation Stations

11.7 KDOQI considers it reasonable to have structured training and supervision of dialysis technicians and nurses before and during their initial cannulation attempts and regular training updates to maintain cannulation competency.

11.8 KDOQI considers it reasonable to support and educate eligible patients on self-cannulation of their AV access (AVF or AVG).

12.2 KDOQI considers it reasonable to use ultrasound to help determine direction of flow and proper needle placement in the AV access of select patients as needed and performed by trained operators to prevent cannulation complications.

ESVS 6.3.2.2. Ultrasound-assisted cannulation. Statement supports ultrasound-assisted cannulation to reduce cannulation difficulties but identifies the need for RCTs of ultrasound-guided cannulation versus unassisted cannulation to determine benefit. The statement also supports ongoing education and training of the dialysis facility staff on cannulation techniques.

POCUS devices are rapidly entering the nephrology market. The full-scale ultrasound devices can have a large footprint and sophisticated controls, leading to a steep learning curve to reach competency. The handheld POCUS devices are a point and image technology. The devices are transportable as the probes typically mate to a smartphone or tablet for the image display. Various cloud-based applications are available for image storage and linkage to the electronic medical record. The cost of the handheld devices has reached a range that allows an individual health care provider to purchase the device and carry it with them like a stethoscope (Table 16.11).

The utilization of ultrasound imaging of the AVF or AVG can assist the dialysis care team with cannulation. Surgeons and interventionists typically utilize ultrasound as a routine part of the vascular access assessment and can create a cannulation map as part of the assessment process. The map becomes part of the patients' medical records and serves as a reference during the cannulation process. A POCUS device can be used in the dialysis facility to create a cannulation map. The cannulation map elements should be documented in a drawing or image of the vascular access and included as part of the patient's medical record. Refer to Table 16.12

TABLE 16.11 Point-of-Care Ultrasound Devices

Brand	Website
Butterfly iQ	https://www.butterflynetwork.com/
Biim linear probe 12-4	https://biimultrasound.com/get-biim/

TABLE 16.12 Cannulation Mapping for the Critical Elements of the Cannulation Map Documentation

POCUS Assessment Element	Purpose
AVF, endovascular AVF or AVG location from anastomosis to the end of the cannulation zone	Identifies the location of the access in a cannulation map for utilization by cannulators or real-time for the cannulator.
Vessel/conduit depth	Determines if the cannulation zone can be reached with a standard 1-in needle. If not, is a shorter or longer needle required? The depth from the skin to the top of the vessel/conduit is measured in millimeters. The depth is then used to determine the best angle of needle entry.
Vessel length in the cannulation zone	Determines the length of arterial and venous cannulation zones. The ability to utilize needle site rotation will then determine if the rope ladder or buttonhole cannulation method should be used in one or both cannulation zones for AVF or endovascular AVF. AVG cannulation method is rope ladder. Should the AVG have a limited cannulation zone, needle rotation must be attempted.
Vessel diameter within the cannulation zone to confirm needle gauge sizing—AVF and endovascular AVF only	Determines the needle gauge the arterial and venous cannulation zones can accommodate. Typically, the same gauge needle is utilized for both arterial and venous sites. Thus, the needle gauge should be the gauge that the smaller vessel diameter can accommodate.
Vessel topography for changes in depth (dips) or location (curves)	The standard AVF fistula needle is metal and requires a straight conduit path to advance the needle without puncturing the back or side wall of the vessel/conduit. The cannulation zone vessel/conduit top must be shorter than the needle length to ensure the entire needle bevel enters the vessel and can be advanced to secure.

AVF, Arteriovenous fistula; *AVG*, arteriovenous graft; *POCUS*, point-of-care ultrasound.

Descriptions of a fixed full-scale ultrasound cannulation station operated by registered nurses have been reported in the literature. Results include a reduction in the number of multiple needle cannulation attempts, infiltrations, or hematoma formations (Table 16.13).

The registered nurse uses the POCUS device to assess cannulation readiness and create cannulation mapping and/or real-time cannulation of new or difficult-to-cannulate accesses. The nurse can assess the maturing AVF or healing AVG for cannulation readiness utilizing the One Minute Check and then visualize the access under ultrasound. Real-time ultrasound-guided cannulation allows the nurse to image the needle entry into the tissue, puncture into the vessel, and needle advancement. The procedure is very similar to the ultrasound guidance of a peripherally inserted central catheter (PICC) line. The cannulation station model equips the nurse with the proper tool to visualize the access and create a plan prior to the cannulation. Typically, the nurse is also the Vascular Access Coordinator, limiting their patient assignments to access-related care and procedures and not the general dialysis treatment oversight.

Cannulation stations can be utilized for initial and difficult vascular access cannulation. The station model can be adjusted to fit within the floor plan of the HD treatment area. The ideal cannulation station is a separate room attached to the HD treatment floor. The station can be staffed by an expert cannulator. The vascular access check or assessment can be done with a time allotment that is separate from the staff member's assignment for the dialysis initiation. The needles can then be flushed with normal saline and adequately secured for the patient transfer from the cannulation station and their dialysis station. The use of a cannulation station room can easily incorporate POCUS. If the floor plan does not accommodate a cannulation station in a separate room, then a phlebotomy chair can be used in an acceptable location. The same process of care is followed as described for the cannulation station room. Infection control measurements must be appropriately utilized at the cannulation station and with the turnover between patients.

The POCUS utilized by the HD staff is not intended for diagnostic purposes but to guide the cannulation process in accordance with the scope of practice of the user (dialysis nurse or patient care technician). The POCUS device itself should be easy to use with a point-and-see mode. Measurements include vessel/conduit depth and diameter to support cannulation. A competency-based training program must be part of POCUS utilization by HD staff. Proper infection control measures must be included in the training. The differences in infection control steps are clearly denoted if utilized for real-time cannulation (such as sterile probe cover and ultrasound gel) compared to cannulation mapping without real-time cannulation (aseptic technique). Color flow Doppler or other flow measurements would be considered diagnostic and out of the scope of practice by the dialysis nurse or patient care technician. Diagnostic POCUS can be utilized by the advanced practice or physician dialysis team members to create the cannulation maps. The surgeon or interventionalist should update cannulation

TABLE 16.13 Studies of POCUS to Reduce Cannulation-Related Complications

Study	Ultrasound Process of Care	Results Without Ultrasound (Landmark)	Results with Ultrasound Guidance
Marticorena R, et al. Real-time imaging of vascular access to optimize cannulation practice and education: role of the access procedure station. ASN poster SA-PO1072 2104	Access procedure station with full-scale ultrasound device	Multiple needle insertions at least once per week over 5 weeks 125 events	Multiple needle insertions at least once per week over 5 weeks 25 events
Carneiro FD, et al. Reducing adverse effects of arteriovenous fistula cannulation with Doppler ultrasound. ASN poster SA-PO1071 2014	Access procedure station with full-scale ultrasound	Hematoma episodes/pt year 2.63 Two cannulation episodes/pt year 4	Hematoma episodes/pt year 1.71 Two cannulation episodes/pt year 1.78
Kumbar L, et al. Coronal mode ultrasound-guided hemodialysis cannulation: a pilot randomized comparison with standard cannulation technique. *Hemodial Int.* 2018;22(1):23-30	Handheld POCUS—bedside	Patient satisfaction with cannulation 82.0%	Patient satisfaction with cannulation 94.6% ($p = 0.04$)
Luehr A. Use of ultrasound guidance during cannulation of arteriovenous fistulas. *Nephrol Nurs J*. 2018;45(5):423-435	Portable full scale POCUS–bedside	Proportion of failure per 1000 cannulations 15.5	Proportion of failure per 1000 cannulations With roll in of the ultrasound rate 9.3, 7.3, and 4.9

POCUS, Point-of-care ultrasound.

map after any surgeries or interventions that might alter the cannulation zones or method (e.g., placement of a stent into the cannulation zones).

POCUS can also be helpful in the home dialysis programs. It can be utilized to assist the patient with self-cannulation or the care partner with cannulation. The home training nurse can also use POCUS to locate veins for blood draws or intravenous (IV) placements as part of the chronic kidney disease (CKD) patient vessel preservation practice.

Note: The complete One Minute Check should be completed prior to the POCUS for cannulation mapping or utilization with real-time cannulation.

Conclusion

The science of cannulation is evolving. Randomized clinic trials are viewed as the proper method to evaluate clinical practice, such as cannulation techniques. A recent multicenter randomized trial to compare buttonhole versus step-ladder (rope ladder) cannulation for home HD failed to reach enrollment numbers and was converted to a pilot study. Barriers to enrollment included the high usage of CVCs in the home HD patient group. Another barrier related to patient or training staff preference for a specific cannulation method. A common documentation issue was also noted as the detailed study cannulation log was not completed by all participants. Thus, cannulation complications data are incomplete.

Barriers to conducting an RCT include the lack of a standardized cannulation documentation tool, variation in local facility policy and procedure, lack of universal adherence to the cannulation policy and procedure, the large number of cannulations, and variability of different cannulators.

The art of cannulation remains a critical element of successful cannulation. Expert cannulators have mastered the art and can be taught science. It is challenging to teach the art element of cannulation to a new learner. The development of better training simulation tools can hopefully address this issue.

Within the nephrology community, the use of self-cannulation must be expanded. The movement toward home HD hinges on the ability of the patient to self-cannulate or the engagement of a care partner to cannulate. The emergence of endovascular AVF is also an opportunity to offer self-cannulation to more in-center HD patients.

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17

Central Venous Access for Hemodialysis

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The Role of Central Venous Access

In the United States, more than 5 million central venous catheters (CVCs) are placed every year, translating to more than 15 million days of treatment with CVCs for different purposes. CVCs are useful tools to administer medications and fluids, and to collect blood samples and exert a pivotal role in the setting of hemodialysis (HD) treatments in patients affected by either acute kidney injury (AKI) or end-stage kidney disease (ESKD). Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) study indicate that 15% of HD patients in the United States are dialyzed with catheters; in other countries, the use of catheters differs significantly, ranging from 45% in Canada to 25% in Italy, 16% in the United Kingdom, and 6% in Japan.

The Kidney Disease Outcomes Quality Initiative (KDOQI) considers arteriovenous (AV) access to be preferable to a CVC in most incident and prevalent HD patients due to a lower risk of infection and an association with lower all-cause mortality. Hence, if not contraindicated, incident HD patients starting dialysis with a CVC should convert to AV access as soon as possible. In a world that counts more than 2 million prevalent patients treated with HD, CVC remains the most rapid method to guarantee kidney replacement therapy when AV access is not immediately available. CVC must provide the prescribed HD treatment with an adequate flow, preferably in excess of 400mL/min. CVCs must guarantee adequate biocompatibility, flexibility, and resistance, remaining chemically neutral. Their function should represent a bridge to more longer-term vascular access, such as an AV fistula (AVF) or AV graft (AVG). The ancillary use of a CVC may be necessary while waiting for a planned living donation of a kidney transplant or in patients undergoing peritoneal dialysis who have to interrupt their treatment for complications. The most common placement sites are the internal jugular, subclavian, and femoral veins, cannulated mainly with the Seldinger technique (see later).

Types of Catheters

The principal types of HD CVCs are tunneled (or cuffed) and nontunneled catheters. The use of tunneled CVCs is preferred due to the lower risk of infections compared with nontunneled CVCs and their better performance in terms of delivered dialytic dose. A recent alternative, used in selected cases, is represented by a hybrid prosthesis-tunneled catheter device, HD reliable outflow—HeRO device, or the Surfacer Inside-Out Access Catheter System. Both these devices are useful for patients with either central venous stenosis or obstruction, two complications occurring in 25% to 40% of patients using CVCs.

Silicone is the main material choice for tunneled CVCs because of its intrinsic softness and flexibility associated with thicker catheter walls. Polyurethane or copolymers, such as polyurethane/polycarbonate (Carbothane), are the prevalent choice for nontunneled ones. Polyurethane has thermoplastic properties that guarantee flexibility, but its synthesis process may also confer mechanical stiffness, pressure strength, chemical stability, and biocompatibility. Polyurethane presents a superior tensile strength than silicone, so CVCs are designed with larger inner lumen maintaining the same outer diameter. This peculiarity improves the overall catheter flow rate and reduces the possibility of catheter fractures in comparison with silicone CVCs. Carbothane presents all the advantages of polyurethane with higher resistance to body fluids, strength, and better biocompatible properties and, for these reasons, is the most commonly used.

Inner CVC configuration depends on the number of lumens, which can be single, double, or triple. Double-lumen CVCs are characterized by cylindric lumens resembling a double O or by a symmetric disposition resembling a double specular D; other double-lumen devices may also have the distal part divided. Other relevant differences among these devices regard the tip, which may be coaxial, split, step-tip, or Z shaped.

Randomized controlled trials and meta-analyses have failed to demonstrate a significant difference between the different types of devices.

Nontunneled Central Venous Catheters

Nontunneled CVCs serve as an emergency tool for dialysis support for AKI and/or in the setting of immediate need of HD. Nontunneled CVCs usually present diameter sizes of 8–13.5 French (Fr) and are generally available in a variety of lengths ranging from 15 to 24cm, according to the cannulation site chosen: right internal jugular and subclavian veins require 15–20cm CVCs, while left internal jugular and subclavian veins require 20–24cm. Similarly, the femoral vein catheter should measure between 20 and 24cm.

Nontunneled CVCs should be used for a limited period, not exceeding 2 weeks, because of their burden of infectious risk and their possible dislocation due to the presence of cutaneous anchoring stitches only. As soon as possible, nontunneled CVCs must be converted into tunneled/cuffed CVCs.

Tunneled Central Venous Catheters

Tunneled CVCs usually present a median length from cuff to tip of 20–50cm. They may be round or flat, with a catheter size typically ranging from 15 to 16F. Tunneled CVCs have a Dacron cuff for subcutaneous anchoring and present different designs of lumens and tips, with or without side holes. Their presence avoids perturbations of blood flow caused by suction effects against either the vein or the right atrial walls but, on the other hand, the hole design confers irregularity to the CVC surface, which may favor thrombosis and infection. Tunneled CVCs represent the main vascular access in patients affected by kidney failure with unknown or very limited life expectancy or when the other AV access sites are exhausted. The age of the patients could be determinant in choosing tunneled CVCs instead of AV access. In particular, they are indicated for elderly subjects (>85 years old) with a higher risk of AVF or AVG access failure or with a condition that could be worsened by their use, such as heart failure with severely reduced ejection fraction due to cardiomyopathy, coronary artery disease, or heart valve diseases. In those cases, there is no maximum time limit for tunneled CVC use. At the same time, they may represent a valid alternative to nontunneled CVC if the period until AVF maturation, live-donor kidney transplant, or in-course of PD-related complications that need PD catheter removal is expected to exceed 2 weeks.

Central Venous Catheter Removal

Tunneled or nontunneled CVCs are removed in case of matured and functioning AV access, as well as kidney function recovery after AKI or successful kidney transplant. Catheters may also be removed in selected cases of late complications, such as catheter-related infection or CVC dysfunction. Tunneled CVC removal is usually performed using cut-down and traction. New removal techniques such as laser extraction and intraluminal CVC dilatation can also safely extract CVC from vessel walls (see "Catheter adhesion").

Central Venous Catheter Placement

Choice of Central Venous Catheter Location

The right internal jugular vein represents the first choice for CVC insertion for several reasons (Table 17.1). First, it is a

TABLE 17.1 Central Vein Approaches for Dialysis Catheters

Priority	Vein	Advantages	Disadvantages or Complications
First choice	Internal jugular vein	• Best with ultrasound • Right side gives more chance to correct blind catheter tip placement	• Medium infection risk • Medium bleeding risk • Uncomfortable when not tunneled
Second choice	Femoral vein	• Lower bleeding risk • No need for radiological control after insertion • Avoid life-threatening risks such as arrhythmias, pneumothorax, hemothorax, hemomediastinum, atrial perforation	• Higher infection risk • Higher thrombosis risk • Poor catheter performance when the patient sits up
Third choice (avoid proximal or terminal AV fistula in the same side)	Subclavian vein	• Lower infection risk • Suitability for subcutaneous tunneling and port access	• Higher bleeding risk • Higher pneumothorax risk • Higher thrombosis risk • "Blind" procedure that cannot be guided with ultrasound

AV, Arteriovenous.

Modified from Santoro D, Benedetto F, Mondello P, et al; Vascular access for hemodialysis: current perspectives. *Int J Nephrol Renovasc Dis*. 2014;7:281–294, Originally published by and used with permission from Dove Medical Press Ltd.

large superficial vein that has easy ultrasound visualization. Moreover, its straight course into the superior vena cava or right atrium, without any corners, reduces the risk of malposition and allows high blood flow for HD. The exception could be represented by a central stenosis or the presence of pacemaker wires.

Normally, the jugular vein lies anterolaterally to the carotid artery, but in a small percentage of patients, the vein is immediately anterior to the artery or even medial to it. If the internal jugular vein lies above the carotid artery, an arterial puncture is a risk to be considered. In order to reduce this risk, a very modest degree of rotation of the head away from the cannulation site may be necessary, at the same time avoiding excessive rotation since it may reduce vein diameter. Ultrasound-guided technique may help to reduce incidental arterial puncture (see later).

On the opposite side, the choice of left internal jugular vein is associated with a higher incidence of CVC dysfunction due to the two right angles that the device has to pass through during its way down to the superior vena cava. Such a tortuous route can cause reduced blood flow rates and greater risk of thrombosis or stenosis due to increased trauma to vessel walls.

Femoral access is considered the second choice due to the higher incidence of thrombotic and infectious complications. It could be preferred in patients with bilateral occlusion of the central thoracic veins, kyphosis, severe pulmonary edema, or in people with an emergent need of vascular access. Otherwise, they are contraindicated in patients with known iliac vessel pathology, major infection risk (such as chronic diarrhea), and morbid obesity (body mass index [BMI] >35 kg/m^2).

Subclavian placement has become less frequent in clinical practice because of the notable risk of central venous stenosis that can compromise future AV access on the same side (Table 17.1).

Alternative locations are represented by inferior vena cava by translumbar puncture, collateral thyrocervical, saphenous vein, or, as a last resort, transhepatic venous access.

The length of the catheter inserted via the right internal jugular vein is typically 15cm, while it should be 20cm via the left internal jugular vein. Ideally, for nontunneled catheters, the tip should lie outside the right atrium, and its position should be checked during the procedure with electrocardiography, or on a postprocedure chest radiograph, before starting HD. For tunneled-cuffed catheters, one of the two tips should lie inside the right atrium. Peres and colleagues elaborated a formula to establish the right insertion of the CVC site (Table 17.2).

This approach was partially modified by Czepizak and colleagues through a prospective study on catheter insertion sites. They identified the right position to place the CVC as follows: height (cm)/10 - 1cm for catheterization of the right internal jugular vein and height (cm)/10 + 4cm for cannulation of the left internal jugular vein.

The "mid-sternal length plus sternoclavicular joints spacing" formula, adopted by Salimi and colleagues in 2020, can be a helpful alternative to inserting tunneled CVCs in the left internal jugular vein: the total CVC length should correspond to the sum of the distance between the insertion point of the needle and the sternal notch, the distance calculated between that point and half-length of the sternum, in addition to the distance lying between the left and right sternoclavicular joints.

TABLE 17.2 Recommended Formula for Catheter Insertion

Vein Cannulation Site	Formula
Right infraclavicular subclavian	(Height/10) - 2cm
Left infraclavicular subclavian	(Height/10) + 2cm
Right internal jugular	Height/10
Left internal jugular	(Height/10) + 4cm

Adapted by Peres PW. Positioning central venous catheters—a prospective survey. *Anaesth Intensive Care.* 1990;18:536-539.

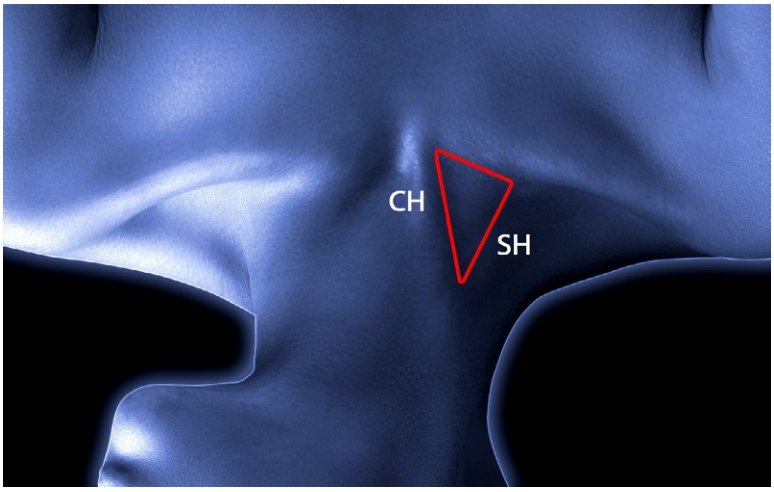
Anatomic landmarks are useful for easily finding the central veins, as in the case of Sedillot's triangle in the neck, which describes the internal jugular vein cannulation area. This triangle is delimited by the clavicle and both sternal and clavicular heads of the sternocleidomastoid muscle. Insertion of the CVC has to be performed through the puncture inside this triangle (Fig. 17.1).

For subclavian CVCs, the anatomic landmark is represented by the clavisternomastoid angle formed by the connection of the lateral head of the sternocleidomastoid muscle and the clavicle, while for femoral placement, the landmark lies approximately 1cm below the inguinal ligament, where the femoral vein runs medial to the femoral artery. Valsalva maneuver can be used in each cannulation approach to increase vein diameter.

Operating Room and Patient Preparation

CVC insertion should be performed in an operating room with adequate equipment and assistance under strict aseptic conditions with full sterile technique. The operator must wear sterile gowns and gloves as well as mask and cap. The room must have immediate access to periodically check emergency resuscitation equipment and medications for the treatment of acute complications.

Adequate informed consent for the CVC placement should be obtained from the patient, based upon a clear understanding of the medical procedure and its implications, limits, and side effects. Preliminary evaluation must include a complete blood count and laboratory assessment of coagulation status, while the patient's preparation includes trichotomy on the site of CVC placement in case of femoral access. The patient should be placed in the Trendelenburg position, with a 10-degree head-down tilt for upper limb CVCs, and in the supine position, in order to increase vein diameter and reduce the risk of air embolism. The external knee rotation is



• **Fig. 17.1** Sedillot's triangle, delimited by the sternal *(SH)* and clavicular *(CH)* heads of the sternocleidomastoid. Inside this triangle is the approximate normal course of the internal jugular vein

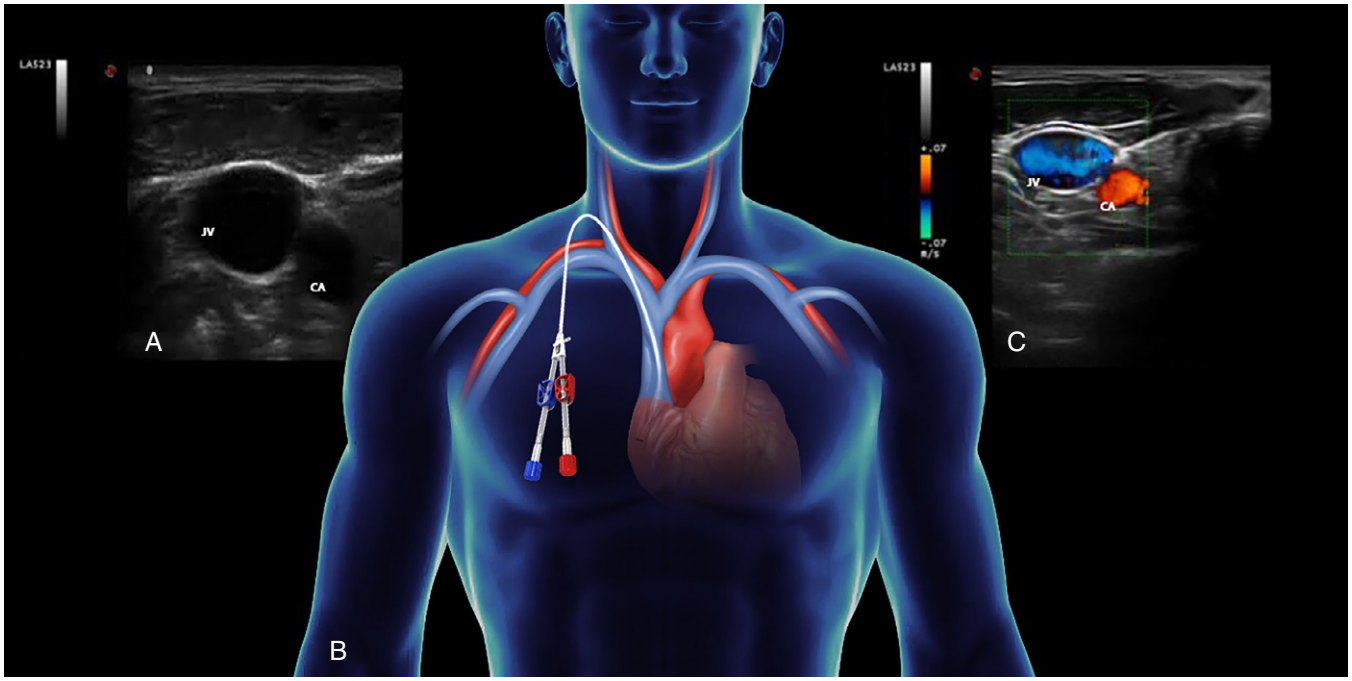
suggested for femoral vein cannulation. During the procedure, oxygen saturation and blood pressure devices must always be available, while continuous electrocardiogram (ECG) monitoring may be used for rapid identification of arrhythmias induced by the guidewire when it touches right atrium walls.

Imaging-Assisted Central Venous Catheter Placement

Even if anatomical references are good landmarks to isolate the proper zone, where to insert CVC, real-time imaging techniques are highly recommended for CVC placement, being positively correlated to better cannulation outcomes and reduced incidence of adverse events.

According to the 2019 National Kidney Foundation (NKF) KDOQI Clinical Practice Guideline, CVCs should be placed by trained operators in centers where ultrasound guidance and/or fluoroscopy are available. Highly qualified fluoroscopic imaging equipment is essential to ensure proper CVC insertion and, at the same time, to guarantee as low radiation emission as possible for both the patient and the medical staff performing the procedure (Fig. 17.2B).

Ultrasound-guided catheter placement should be performed for all tunneled CVCs since it has demonstrated a higher success rate on the first attempt compared with the anatomic approach (86% vs. 55%, respectively). An ultrasound study should be performed to assess vein and artery location (see Fig. 17.2A). In particular, vein collapsibility



• **Fig. 17.2** (A) B-mode and (C) Doppler ultrasonography assessment of carotid artery and jugular vein before central venous catheter (CVC) placement. (B) Correct CVC placement in right internal jugular vein.

under transducer pressure and its typical wave pattern at Doppler ultrasound evaluation help the clinician to identify the vessel correctly (see Fig. 17.2C).

After examination of the venipuncture site, the sterile field should be prepared, the skin cleaned with iodine solution, and the transducer has to be covered with a sterile protection bag. Two main approaches are typically used:

- out-of-plane approach, with the ultrasound probe placed on the short axis in transversal position in relation to the vein; and
- in-plane approach, where the transducer is positioned on the long axis.

A solution of 1% lidocaine is generally used as local anesthetic infiltration before the venipuncture. Once the vein has been selected with ultrasound imaging, the next step is cannulation with the Seldinger technique. The operator uses a needle applied on a 10-mL syringe filled with 3–4mL of saline solution, placed at a 45-degree angle to the skin. Once the needle is inside the vessel, the guidewire can be inserted through the needle. After a small superficial incision on the skin, a dilator is passed over the wire while the operator holds it close to the tip with a rotating motion. For nontunneled CVC placement, once the dilator is removed, the catheter is advanced over the wire up to the superior cavoatrial junction and anchored to the patient's skin with silk suture points (usually 2-0) or with adhesive-based securement devices such as Grip-Lok, StatLock, or similar (Fig. 17.3).

Tunneled CVCs need further vein dilation after the first dilator passage over the wire, with a peel-away introducer provided with an incorporated valve to prevent gas embolism. A tunneled CVC requires a subcutaneous cuff at approximately 3–3.5cm from the insertion site, which allows a fibrous sealing of the skin that acts as a mechanical barrier against infections.

When the device is in place, the reflux test can be performed, flushing both ports with 10mL of saline solution to test any resistance. If there is no blood return through the CVC, the success rate defined as functional use is only 53%. In this case, the CVC must be immediately repositioned and retested for flushing. If the reflux test is positive, the catheter can be sutured to the skin or as an alternative, stabilized with subcutaneous devices such as SecurAcath. In order to prevent infections, after cleaning the CVC insertion site, the device can be dressed with transparent bio-occlusive dressing with or without clorexidine (Fig. 17.4).

Postinsertion imaging should be considered to avoid undesired CVC malposition that can lead to acute major adverse events or dysfunction. The use of postprocedural chest x-ray can not only confirm the correct location of the CVC but also can identify potential complications such as hemothorax or pneumothorax.

ECG-Assisted Central Venous Catheter Insertion

The ECG-assisted technique was recently demonstrated, in a recent meta-analysis including 1672 patients, to be more accurate in evaluating correct placement of CVC than the traditional x-ray method. Intracavitary ECG guidance consists of placing an electrode on the wire to monitor the P-wave morphology on the ECG monitor while the CVC is slowly advanced toward the superior vena cava. When the device reaches the right atrium wall, there will be a negative deflection of P-wave on lead II. Proper positioning of the device at the cavoatrial junction is thus reached gradually, withdrawing the CVC until the visualization of the maximal P-wave.

The study of Yu-Xia Yin and colleagues on 2250 adult patients demonstrated a first-attempt successful tip location rate of 92% with ECG-assisted technique versus 79% observed in the control group of CVCs implanted through anatomical landmark guidance. Moreover, postprocedural chest x-rays showed that the correct tip location in the study group had a sensitivity of 99% versus 87% observed in the anatomical landmark group.

• **Fig. 17.3** A nontunneled central venous catheter placed in the right internal jugular vein.

• **Fig. 17.4** A tunneled central venous catheter placed in the right internal jugular vein.

An alternative to this method is represented by the use of dedicated ECG monitors, such as the Sherlock-3CG. This device utilizes a magnetic-based tip navigation system combined with an ECG-based tip location system.

Central Venous Catheter Complications

Acute Placement-Related Complications

Inadequate CVC placement for HD can result in acute complications in 5% to 19% of cases. The risk of poor positioning depends mainly on the operator's experience, the choice of the insertion site, image-guided placement (either with fluoroscopy or ultrasonography [US]), and peculiar patients' morbidity that can affect the procedure. In people with pacemakers or defibrillators, the first step in avoiding predictable complications is to choose a cannulation site opposite to the implanted device whenever possible. CVC placement in the same central vein is associated with a higher risk of thrombosis and superior vena cava syndrome.

Bleeding through the cutaneous entry site is one of the most common complications, often due to high venous pressure. Vascular injury may include arterial puncture and the development of pseudoaneurysm or AVF. Due to the proximity of arteries and veins, accidental arterial puncture may be a risk during CVC placement, especially in the femoral vein. However, the complications are much more severe during cannulation of the subclavian vein because both arteries and veins are located under the clavicle and cannot be compressed manually, thus leading to hemothorax in severe cases. Also, the risk of pneumothorax is higher in the subclavian approach due to the proximity of the pleura to the cannulation site, with a reported incidence rate of 2%–3% of cases.

Perforation of a central vein is a potentially life-threatening complication caused by traversing the vessel wall with the dilators during the insertion procedure. Careful insertion of the dilator through the guidewire without forcing its advance to prevent kinking and the use of real-time fluoroscopic imaging techniques make this complication very unlikely.

A rarely reported but serious complication is the development of carotid-jugular fistula, which is associated with atherosclerotic embolism and ischemic stroke.

Gas embolism has been a complication due to the thickness of the introducers, but hemostatic valved peel-away technology helps avoid this complication. Trendelenburg's position of the patients may also decrease the risk while carefully replacing the introducer dilator by the CVC.

Postplacement Complications

Causes of CVC dysfunction occurring during the first dialysis session are usually related either to CVC tip dislocation or to kinking. Jugular tunneled CVCs, for example, are secured by the cuff to the subcutaneous tissues, but orthostatic or seated position of the patient implies a downward movement of the chest and a consequent catheter retraction. The eventuality of an internal jugular CVC tip situated in the superior vena cava or at the cavoatrial junction is more frequent in obese patients with large breasts or in left side placement and needs to be corrected with an imaging-guided procedure or replacement with a longer catheter. CVC kinking is a complication usually caused by tunneling. For internal jugular veins, the curve should lean on the clavicle, and kinking can be suspected if there is resistance to aspiration soon after insertion. If the replacement of tunneled CVC with the reintroduction of the metal guide is not feasible, it must be done through a new subcutaneous tunnel.

Subclavian catheter pinching and its fracture due to the costoclavicular clamp are quite uncommon, with possible embolization of fragments toward cardiac cavities or pulmonary arteries. It is more frequent with smaller CVCs for therapies.

Nontunneled catheters, in particular after prolonged use, can be responsible for atrial perforation, cardiac tamponade, and hemothorax, both because of their rigidity and a tip placement leaning on atrial or superior vena cava walls. For this reason, Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend their removal after 2 weeks or converting into tunneled/cuffed CVCs.

Catheter Dysfunction

CVC dysfunction, along with infections, is one of the most important causes that reduce CVC survival. In 2019, NKF KDOQI Clinical Practice Guidelines defined dysfunction as the inability to maintain the prescribed extracorporeal blood flow required for adequate HD without lengthening HD treatment. The previous KDOQI edition stated as acceptable a value of >300mL/min and a negative arterial pressure (Pa) up through 250mm Hg. A decrease in conductance, intended as a ratio of blood pump flow to prepump pressure (QB/Pa) >10%, can suggest early a dysfunctional catheter, while the ball-valve effect, in which CVC lumen can receive flow but blood aspiration is impaired, is a late sign.

An observational study of a total of 1,075,701 CVC HD patients showed that 65% of the patients had at least one session with catheter dysfunction, and multivariable analysis demonstrated that catheter dysfunction was associated with a higher odds of missing an HD session due to access problems (odds ratio [OR], 2.50; $p < 0.001$), having an access-related procedure (OR, 2.10; $p < 0.001$), and being hospitalized (OR, 1.10; $p = 0.001$).

However, the previous KDOQI expert opinion–based recommendation was interpreted by nephrologists as being necessary to maintain blood flows >300mL/min to ensure adequate HD, even if it necessitated running CVCs in the reverse configuration with an associated risk of recirculation or administering thrombolytic agents. Conversely, low-body-weight patients or those receiving frequent HD could

obtain adequate Kt/V with a mean blood flow prescription of 250–300mL/min. There are also intrinsic differences in recirculation rate based on catheter length and the site of placement in the femoral rather than the internal jugular vein, ranging from 10% to 4% with 24-cm CVCs. Moreover, patients may undergo single episodes of dysfunction due to transient factors such as higher values of hemoglobin, interdialytic weight gain, blood pressure drop, or even the assumed position during HD sessions.

Central Venous Stenosis

Central venous stenosis is ascribed to mechanical stress on vessel walls as well as to infections and is more common in patients bearing nontunneled subclavian CVC (42%–50% of cases) and less frequent with jugular (0%–10%) or tunneled CVC. Stenosis risk may be reduced if the catheter is inserted centrally in a large caliber vein providing a high blood flow and not lying on the confluence of other veins. Patients complain of an increasing edema localized to the upper limb ipsilateral to the catheter, secondary to higher venous pressure. For this reason, also AVF placement on that limb must be avoided because it also exacerbates venous blood return. Late signs include the development of collateral veins, phlebitis, stasis ulcers, and a higher rate of infections on the involved limb, as well as pleural effusion and signs of intracranial hypertension. Stenosis can be treated with angioplasty and stent placement in distensible central vein lesions or if they recur within 3 months. Other surgical treatment options include bypass involving the axillary vein and, alternatively, axillary, jugular, or femoral vein, or an axillary-atrial bypass.

Central Venous Catheter-Related Thrombosis

Late CVC dysfunction is generally due to thrombotic phenomena depending on multiple factors, among which, the catheter site with a higher risk from internal jugular to subclavian and even more, femoral vein. Also, low and turbulent blood flow, as well as a patient's predisposition to coagulopathy, can worsen thrombosis. Symptoms also differ depending on CVC placement, with worse outcomes for femoral venous thrombosis, which may lead to pulmonary embolism. A radiologic assessment is required to exclude central venous stenosis or CVC-related thrombosis. It may include venography with contrast injection through the catheter lumen. Briefly, CVC-related thrombosis can be grouped as:

- Intrinsic thromboses. These are usually characterized by catheter tip thrombi, which may act as a valve allowing fluid infusion but not their aspiration from the CVC or intraluminal thrombi due to low blood flux. The fibrin sheath represents a peculiar form of thrombosis developing around the catheter starting from 24 hours after its placement. It is a reactive deposition of fibrinogen, fibronectin, lipoproteins, albumin, and coagulation system factors progressively expanding from the point of the vessel wall touched by CVC to cover the entire catheter intravascular surface. It represents the leading cause of CVC dysfunction (40% to 100% of catheters), with difficulty in both injecting and aspiring fluids through the port. Moreover, fibrin sheath has a strict connection with biofilm formation on the CVC's outer surface, which can favor both clinically relevant catheter-related infections and thrombosis.
- Extrinsic thromboses. Usually represented by mural thrombus located in the superior or inferior vena cava or right atrium, requiring systemic anticoagulation and CVC removal, with a new venous access required. In this case, the patient complains of pain, edema, and collateral circulation may develop.

Catheter Adhesion

Tunneled CVCs can get firmly fixed to the vein wall due to a capsule of fibrin, collagen, and endothelial cells that retains the catheter. Thus difficulty in withdrawal is due to the length of time in place (range between 12 and 120 months) and the narrow caliber of the veins used. Tunneled CVC can be removed by dissecting adhesion at the exit site, along the subcutaneous cuff, or at the entry point in the vein, avoiding excessive traction, which may lead to vascular lesions, rupture of CVC, and embolization in the right atrium or pulmonary artery. Alternatively, interventional radiologists can dilate the vein with an angioplasty balloon introduced by CVC lumen. If it is decided not to remove it, the intravascular portion can be retained, with the risk of thrombosis, embolism, or infection. In such cases, there are no indications for anticoagulant or antibiotic prophylaxis.

Prophylactic Approaches to Maintain Central Venous Catheter Patency

Prophylactic strategies to maintain CVC patency and reduce infectious risk include the adoption of local lock solutions for priming in both arterial and venous ports or the application of neutral-valve closed-system connectors (Tego Needlefree Hemodialysis Connector or ClearGuard HD Antimicrobial Barrier Caps).

Most common lock solutions for the interdialytic period are heparin and citrate. Heparin is a glycosaminoglycan binding antithrombin III, which enhances its physiologic antagonist role counteracting the effects of thrombin and factor Xa. The heparin–antithrombin–thrombin complex thus inhibits fibrinogen to fibrin conversion, thus blocking the coagulation cascade. Heparin 5000 IU/mL is the standard concentration of lock solution injected into each port in different volumes as indicated by CVC manufacturers to fill all the catheter lumens without leaking into the systemic circulation, which represents a possible complication and can predispose bleeding of the patient. Although less common, this use of heparin may be complicated by heparin-induced thrombocytopenia.

Citrate has been proposed as an alternative to heparin because of its anticoagulant and potential antibacterial properties. Citrate acts by blocking calcium-dependent

enzymes of the coagulation cascade by binding to calcium ions, but calcium citrate is rapidly metabolized to bicarbonates if it leaks into the patient's circulation, thus reducing bleeding risk. Citrate 5% lock solution has been used with comparable results to heparin 5000 IU/mL in terms of CVC patency. A higher concentration of trisodium citrate (46.7%) has been withdrawn because of the risk of arrhythmias and a case of fatal cardiac arrest.

Taurolidine is a derivative of amino acid taurine, with an antimicrobial activity including against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant Enterococci. Its methylated derivative seems to interfere with bacterial walls and reduces bacterial adhesion on human epithelial cells in vitro. A multicenter randomized controlled trial on newly positioned tunneled CVCs evaluated the adoption of citrate 4% lock solution after each HD session versus a combined solution of citrate 4%, taurolidine 1.35%, and heparin 500IU/mL (TauroLock-Hep500) twice per week and citrate 4%, taurolidine 1.35%, and urokinase 25,000 IU (TauroLock-U25,000) once a week. Winnicki and colleagues compared CVC dysfunction rates, which were significantly lower in the taurolidine group (18.7 vs. 44.3 per 1000 CVC days), as well as alteplase rescue need was higher in the citrate group (9.8 vs. 3.8 per 1000 CVC days). The taurolidine group also showed a lower rate of CVC-related infections (0.67 vs. 2.7 episodes per 1000 catheter days; incidence rate ratio, 0.25; 95% confidence interval [CI], 0.09–0.63), thus obtaining also significant cost savings comparing overall expenses per patient/year with the citrate group.

According to the 2019 NKF KDOQI Clinical Practice Guideline, recombinant tissue plasminogen activator (r-TPA) may be used as a CVC lock solution once per week as a prophylaxis to reduce CVC dysfunction. On the contrary, there is no favorable evidence to adopt antiplatelet agents or systemic anticoagulants such as warfarin for the prevention of CVC malfunction. Moreover, the high risk of inducing calciphylaxis in end-stage renal disease (ESRD) patients on dialysis should preclude the use of warfarin without any other therapeutic indications. Indeed, warfarin interferes with the activity of matrix gamma-carboxyglutamate Gla protein (MGP) by inhibiting vitamin K–dependent carboxylation reaction, which may worsen systemic calcification.

Bonkain and colleagues compared Tego Needlefree Hemodialysis Connector to trisodium citrate 46.7% lock solution, but no significant differences were noted in terms of both CVC dysfunction rate and bloodstream infections (BSIs). More recent studies were mostly aimed to evaluate the protective role of these connectors against BSI rather than their antithrombotic effects. Hymes and colleagues evaluated the adoption of ClearGuard HD Antimicrobial Barrier Caps versus standard CVC caps with similar baseline positive blood culture rates between both groups, and concluded a protective role of the closed connector system, with 56% lower BSI rate (0.26 BSI detected in the ClearGuard HD caps group vs. 0.59 per 1000 CVC days, respectively; $p = 0.01$). A recent cluster-randomized, open-label, prospective study by Brunelli et al. evaluated ClearGuard HD caps (826 patients) versus Tego plus Curos disinfecting caps (845 patients), and the ClearGuard group had a lower BSI rate (0.28 vs. 0.75 positive blood cultures per 1000 CVC days, respectively; $p = 0.001$).

Treatment of Central Venous Catheter Dysfunction

Thrombolytic agents enhance the activation of proenzyme plasminogen to plasmin, which in turn degrades fibrin deposits. When they are used as lock solutions into CVC lumens, according to instructions from the catheter manufacturers, they do not affect systemic coagulation, and the international normalized ratio (INR) and partial thromboplastin time (PTT) are unchanged. Recombinant tissue plasminogen activator (tenecteplase, alteplase, and reteplase) binds fibrin, and this complex has a great affinity for plasminogen. Tenecteplase, in particular, has the highest fibrin specificity and also shows a better resistance to the physiological inactivation by plasminogen activator inhibitor-1 (PAI-1), compared to alteplase, which has a limited half-life of 3–4 minutes, and reteplase, which is the most economic recombinant tissue plasminogen activator but is also the least fibrin-specific. Urokinase binds directly to the plasminogen to activate it.

Direct comparison performed by Pollo and colleagues among 100 patients receiving long-term HD treated with alteplase 1mg/mL or urokinase 5000 IU/mL demonstrated no significant differences in their tunneled CVC patency (defined as Qb >200mL/min after dwell).

High-dose alteplase (2mg) was more efficient than low-dose alteplase (1mg) in a dwell time of 30 minutes in terms of longer time interval before CVC withdrawal for thrombosis recurrence (10% vs. 19%, respectively), with a mean catheter survival of 955 days versus 782 days ($p = 0.02$). Similarly, high-dose urokinase (100,000IU) was compared to low-dose urokinase (25,000IU) CVC lock, in patients already treated with warfarin for CVC dysfunction. Higher urokinase dosage was effective in 100% of cases treated versus 14% of patients in the low-dose group, and the number of patients who required additional urokinase treatment for more than two HD sessions was 3% versus 48% ($p = 0.01$).

Fibrin sheath, in particular, may require a CVC replacement. While there are no recommendations about CVC stripping as a more effective procedure than fibrinolytic administration, the association of angioplasty to fragment fibrin sheath and of over-the-wire CVC exchange is, at the moment, the most successful strategy in terms of catheter patency.

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18

Noninfectious Complications From Vascular Access

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Noninfectious complications of hemodialysis vascular access are associated with higher morbidity and can be life-threatening. The resulting interruption in the dialysis schedule with inadequate hemodialysis therapy decreased sense of well-being, and overall poor quality of life can lead to frustration amongst patients and their caregivers. Two commonly used long-term hemodialysis vascular accesses are arteriovenous fistula (AVF) and arteriovenous graft (AVG). AVF is preferred over AVG for its lower risks of stenosis and infection, longer patency, and overall lower maintenance cost. However, it may not always be the right choice. In keeping with a patient-centric approach, selecting the right access for the right patient remains practical and is recommended by the 2019 Clinical Vascular Access Guideline from National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-KDOQI). In this chapter, we provide a broad overview of the noninfectious complications of a long-term dialysis vascular access by categorizing them into perioperative, local, and systemic complications (Table 18.1). The noninfectious complications arising from a central venous access are discussed in Chapter 17.

Perioperative Complications

Complications generally arising immediately after and up to 30 days in the postoperative period are often related to the surgery and require immediate surgical attention to minimize long-term sequelae.

Neuralgia

Neuralgia from access construction occurs due to direct injury to adjacent nerves or ligation/clipping of a small cutaneous nerve. The patient with neuralgia may experience severe pain during needle cannulation or develop chronic pain and dysesthesias in the scar tissue overlying an access conduit. Frequently, vascular ischemia may manifest with neuropathic pain, which, if left untreated, can result in protracted ischemic neuropathy.

Seroma/Lymphocele Formation

Peri-graft seroma is a troublesome complication generally limited to AVGs. The exact etiology remains unknown but results from exudation of sterile serum, most frequently confined around the arterial anastomosis of the conduit. Lymphocele can occur from disruption of lymphatics during dissection to expose the artery and vein for anastomosis. Poor skin preparation and possible contact between graft and povidone-iodine or alcohol are believed to be causative factors. Patients with protein-energy wasting and hypoalbuminemia may be prone to seroma formation. Treatment options include simple aspiration to surgical exploration with ligation of leaky lymphatics.

Acute Hematoma/Aneurysm

Acute hematoma formation around anastomosis in the immediate postoperative period is a surgical emergency secondary to dehiscence of sutures and requires immediate surgical attention. Acute dilatation of the vessel, mainly around the arterial anastomosis, could result from arterial wall dissection. Although this complication is infrequent, if neglected, it can result in limb loss or even death (Fig. 18.1).

Acute Arteriovenous Graft Hypersensitivity

Erythema and edema around a newly placed AVG are not uncommon. The redness over the tunnel may be associated with pain and edema, often mimicking infection. An experienced examiner will be able to differentiate between infection and an allergic reaction. The presence of edema and erythema may delay the usability of an early cannulation AVG.

Ischemic Monomelic Neuropathy

Injury to the vasa nervosa leading to infarction of the forearm nerves soon after access creation causes ischemic monomelic neuropathy. Symptoms suggestive of ischemic

TABLE 18.1 Overview of Noninfectious Complications of Hemodialysis Vascular Access

Perioperative complications

- Seroma/lymphocele/hematoma
- Acute thrombosis
- Acute arteriovenous graft (AVG) cutaneous hypersensitivity
- Ischemic monomelic neuropathy

Local complications

- Prolonged bleeding
- Carpel tunnel syndrome
- Hemodialysis access–induced distal ischemia (Steal syndrome)
- Aneurysm/pseudoaneurysm
- Fatal access hemorrhage

Systemic complications

- High output cardiac failure
- Pulmonary hypertension
- Venous hypertension—central vein stenosis
  - Cardiac implantable electronic devices (CIEDs)
  - Multiple central venous catheters
- Posttransplant hyperdynamic circulation

monomelic neuropathy include a classic triad of acute-onset deep burning pain, weakness, and sensory changes in an otherwise warm forearm and hand. Distal sensory impairment with paresthesias and numbness is seen in the distribution of all three nerves (ulnar, median, and radial) of the forearm. On examination, an obvious finding is weakness or paralysis of the muscles innervated by the forearm nerves with patients presenting with a wrist drop (radial nerve), difficulty with adduction and abduction of fingers (ulnar nerve), or difficulty with thumb movements (median nerve). A "claw-hand" deformity with severe neuropathic pain in the immediate postoperative period is pathognomonic of ischemic monomelic neuropathy. Treatment options are limited once ischemic monomelic neuropathy is suspected. The vascular access has to be ligated immediately to minimize the ischemic injury and improve the probability of neurologic recovery.

Local Complications

Complications limited to the extremity with a dialysis vascular access can be categorized as local. The most common noninfectious complication is stenosis in the access circuit secondary to neointimal hyperplasia. The resultant reduction in blood flow and thrombosis leads to interruption in hemodialysis treatment. Stenosis frequently recurs, requiring a robust monitoring and surveillance program to diagnose a dysfunctional vascular access. Most frequently used treatment options include percutaneous balloon angioplasty and stent placement. Unfortunately, repeated endovascular interventions are needed as stenosis tends to recur. Details about stenosis-related access dysfunction and its management are discussed in Chapter 17.

Prolonged Bleeding

Vascular access puncture site bleeding is a source for chronic blood loss and patient discomfort often complicated by

• **Fig. 18.1** (A) Pseudoaneurysm in a forearm arteriovenous graft. (B) Aneurysm at frequent needle puncture sites with shiny depigmented skin. (C) Multiple enlarging aneurysm in a brachiocephalic arteriovenous fistula. (D) Postop hematoma. (E) Postop large hematoma.

delayed hemostasis. The common practice of using heparin during hemodialysis, oral anticoagulation, and antiplatelet therapy results in iatrogenic coagulopathy requiring close monitoring post needle withdrawal. During compression of the needle sites, it is essential to maintain balance between achieving hemostasis without increasing the risk of access thrombosis. The goal is best achieved by using appropriate manual compression without occluding the flow underneath the fingers. Patients and dialysis personnel patients can be empowered and taught this simple task. Most needle puncture sites will achieve hemostasis within 15 minutes of compression.

An access puncture requiring more than 30 minutes of compression to achieve hemostasis is considered problematic and warrants closer evaluation for a treatable cause.

The most common causes for prolonged access site bleeding include a poor cannulation/needle withdrawal technique, cannulating through an aneurysm/pseudoaneurysm, localized infection, outflow stenosis resulting in venous hypertension, and excessive anticoagulation. A thorough review of dialysis circuit pressures, physical examination of the access, cannulation/decannulation technique, and timely referral for imaging studies and/or evaluation by a vascular surgeon can prevent catastrophic outcomes such as access thrombosis or fatal hemorrhage.

Carpal Tunnel Syndrome

Median nerve compression at the wrist causes neuropathy that manifests as constant pain, numbness, and tingling in the thumb, index, middle, and half of the ring finger and thenar region of the palm. The pain tends to worsen during dialysis and, if untreated, can result in muscle weakness manifesting as inability to oppose the thumb and index finger. The thenar prominence of the palm loses its tone and appears flaccid. The incidence of carpal tunnel syndrome has been reported to be around 9%. Comorbidities that increase the risk include diabetes mellitus and ischemia secondary to vascular access surgery. High-flow fistula and steal syndrome are the most important differential diagnoses in a patient who presents with hand pain. Other possibilities include cervical spine disease with root compression and neuropathy related to systemic diseases. Nerve conduction velocity test and imaging of the cervical spine can help confirm the diagnosis.

Treatment of carpal tunnel syndrome depends on the severity of the symptoms experienced by the patient. A conservative approach of wearing a wrist splint and minimizing activities that aggravate pain is preferred when symptoms are mild. Surgical decompression, often an outpatient procedure, is recommended if symptoms progress. Vascular access closure is rarely necessary. Preventive strategy with counseling and education regarding adherence with dialysis therapy can minimize the risk of median nerve entrapment, especially in patients who are unlikely candidates for kidney transplantation.

Hemodialysis Access–Induced Distal Ischemia

After a communication between an artery and vein is created, the blood flow destined to perfuse the distal extremity is diverted into the vascular access. Distal hypoperfusion is prevented by the collateral blood flow. The hypoperfusion and distal ischemia of the hand and fingers result from the lack of adequate compensatory collateral circulation and are classified as hemodialysis access–induced distal ischemia (HAIDI). The other terminology often used is dialysis access–related steal syndrome (DASS). The time of onset can be within 24 hours of access creation to months or years later. The prevalence varies based on the location of the anastomosis between 0.25% and 20%. The incidence is higher with upper arm vascular access compared to forearm. Other risk factors include female gender, advanced age, diabetes, history of peripheral vascular disease, multiple prior vascular access procedures, use of brachial artery for anastomosis, and high access blood flow. The diagnosis is made based on the signs and symptoms and clinically differentiated into three stages from mild to severe (Table 18.2; Fig. 18.1).

Two main treatment goals of HAIDI are improving distal perfusion and preserving the vascular access. The choice of treatment should be based on the clinical features, overall comorbidities of an individual patient, type of vascular access, and its blood flow. Conservative measures such as reducing the pump speed and using warm gloves may be enough to treat mild disease as in stage 1. Moderate to severe disease may require definitive surgical or endovascular intervention. Therapeutic intervention is planned based on the underlying pathophysiology. Patients with high-flow access may benefit from a flow-limiting open surgical or endovascular flow reduction procedure to band the inflow segment of the vascular access. Endovascular technique is minimally invasive and precise. The ultimate goal is to reduce the access blood flow to around 1200 mL/min.

Patients with severe peripheral arterial disease may require diverting the flow with surgical intervention as simple flow reduction procedures may be inadequate. Several surgical options are available to bypass the blood flow into the distal arterial circulation. The most frequently used procedures are revision using distal inflow (RUDI) and proximalization of arterial inflow (PAI). A third procedure called distal revascularization with interval ligation (DRIL) remains an option in select cases. A detailed description of these procedures is beyond the scope of this chapter, and readers are referred to the suggested reading section at the end of this chapter. In extreme situations, ligation of the vascular access may be the only viable option to salvage the extremity.

Aneurysm and Pseudoaneurysm

Aneurysm is defined as a dilated segment of a vessel and includes all three layers of the vessel wall. A pseudoaneurysm is a defect in the vessel or synthetic material walled off by surrounding fibrous tissue. So essentially, an aneurysm can

TABLE 18.2 Signs, Symptoms, and Stages of Hemodialysis Access–Induced Distal Ischemia (HAIDI)

Signs and Symptoms	Stages	Treatment
Cold hand Pallor	Stage 1: Cold, pale cyanotic hand/fingers	Stage 1: Conservative approach, gloves, reduce pump speed
Cyanosis Diminished sensation Ulceration/gangrene Decreased capillary filling Diminished radial and ulnar pulses, which augments on occlusion of the access Basal digital pressure < 60 mm Hg or digital brachial index < 0.4	Stage 2: Hand pain during hemodialysis or with exercise Stage 3: Rest pain, ulcers, necrosis, or gangrene	Stages 2 and 3: Surgical or endovascular intervention as appropriate - Flow reduction intervention for high flow access - Surgical options—RUDI, PAI, DRIL - Ligation of access in extreme situation to prevent limb loss

DRIL, Distal revascularization-interval ligation; *PAI*, proximalization of arterial inflow; *RUDI*, revision using distal inflow.

develop only in native vessels (vein or artery), while a pseudoaneurysm can develop in AVF and AVG. Aneurysm and pseudoaneurysms can develop anywhere along the entire course of access circuit. The incidence of aneurysm/pseudoaneurysm in a dialysis circuit remains undefined as a significant number of these accesses remain stable and functional. There is no clear accepted definition of an aneurysm in a dialysis circuit. The most acceptable definition is enlargement of all three layers of a vessel to roughly three times the diameter of a mature outflow vein. Conceptually, a normal abdominal aorta has a diameter of approximately 2 cm, and an abdominal aortic aneurysm is considered critical for intervention when the diameter is 5.5 cm (less than three times its diameter). However, the natural history of dialysis access aneurysm/pseudoaneurysm remains ill-defined with inappropriate acceptance as "normal and expected finding" by both patients and dialysis care providers.

The combination of hemodynamic changes from access creation and the repeated puncture during dialysis and proximal or central vein stenosis are key risk factors. Same-site needle cannulation can lead to disruption of the vessel wall, which heals with fibrous tissue. The use of rope ladder needling technique for cannulation can minimize the risk of aneurysm/pseudoaneurysm formation. The diagnosis is primarily based upon physical examination and confirmed with ultrasonography. Assessment of the access before each hemodialysis session for increment in size of the aneurysm/pseudoaneurysm, breaks/ulcers in the overlying skin, depigmentation, or shiny paper-thin skin and documentation of the dimensions every 3 months can help differentiate between stable and unstable dilated vessel and guide the treatment plan (Fig. 18.2).

The treatment goals should focus on correcting the precipitating factors such as proximal stenosis, maintaining access function, and preventing complications like blood loss/rupture, thrombosis, and unnecessary transition to central venous catheters. Definitive treatment of an aneurysm/pseudoaneurysm involves either surgical revision of an access (aneurysmorrhaphy or resection with interposed native or synthetic graft) or endovascular therapy with a covered stent graft. The timing for definitive intervention remains largely dependent on the dialysis team's experience, the availability of technical skills, and willingness by the patient to undergo additional surgical procedures.

• **Fig. 18.2** Distal Ischemia as a Consequence of Steal Syndrome. Stage 1: Pale/blue or cold hand without pain. Stage 2: Pain during exercise or HD. Stage 3: Rest pain. Stage 4: Ulcers/necrosis/gangrene.

Fatal Access Hemorrhage

Fatal access hemorrhage is a catastrophic complication secondary to rupture of a neglected enlarging aneurysm/pseudoaneurysm in a dialysis circuit. Often, the overlying skin is necrosed and infected. The complication requires a special mention as it is a preventable event. A general lack of awareness among all dialysis stakeholders, underreporting in literature, and risk of immediate exsanguination mandate implementing broad strategies to avoid a preventable death. The exact incidence remains unknown as most fatal bleeds occur outside a dialysis facility. Educating the patient and their families about the critical and life-threatening nature of the complication is key to ensuring that the patient reaches a hospital emergency room in a timely manner. Simple measures such as asking the patient to keep a Velcro-strap tourniquet handy at home, in the emergency first-aid kit in the car, and at various nursing facilities can help prevent a fatal outcome.

Systemic Complications

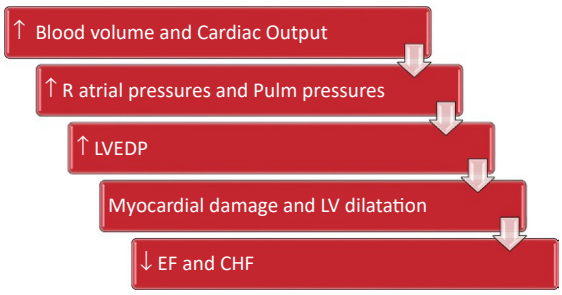
The hemodynamic changes due to dialysis vascular access surgery are often irreversible even after a successful kidney transplantation. Cardiac and pulmonary complications limit the patient's ability to perform routine daily activities without discomfort.

High Output Cardiac Failure

Typical blood flow (Qa) in a vascular access varies based on its location. A minimum blood flow of 600 mL/min is required to support maintenance hemodialysis. Generally, the blood flow of an arteriovenous access ranges between 800–1000 mL/min in the forearm and 1000–1500 mL/min in the upper arm. A high-flow access is defined as a blood flow of more than 2000 mL/min. The prevalence of high-flow access is underestimated in literature as the concept remains underappreciated by the dialysis community. The reported prevalence ranges from 9% to 20% of the prevalent hemodialysis population and does not depend on the type of vascular access. The risk factors for developing high-flow vascular access include upper arm access, male sex, relatively large arterial anastomosis, and previous access surgery.

High-flow vascular access can lead to high output cardiac failure, which is suspected with symptoms of dyspnea, reduced exercise tolerance, and signs of pulmonary edema despite adherence with hemodialysis treatment and minimal interdialytic weight gain. Clinical signs include wide pulse pressure, tachycardia, cardiomegaly on chest x-ray, resting cardiac output (CO) of >8 L/min or a cardiac index of >3.9 L/min/m^2, and low systemic vascular resistance.

A high index of suspicion is essential to diagnose high output cardiac failure secondary to high-flow vascular access. Patients with preexisting ischemic or valvular cardiac disease or New York Heart Association (NYHA) Class IV heart failure may be unable to sustain cardiac remodeling necessary to maintain adequate stroke volume. The diagnosis is confirmed with the elicitation of a simple bedside Nicoladini-Branham sign, which involves manually compressing the access for 30–60 seconds with a reduction in heart rate, an increase in systemic blood pressure, and a decrease in CO. On two-dimensional echocardiography, the cardiac stroke volume improves with occlusion of the access. Estimating an access blood flow-to-CO ratio (Qa:CO) of >0.3 has been associated with high output cardiac failure (Fig. 18.3).



• **Fig. 18.3** Long-Term Cardiac Effects of Arteriovenous Access. *CHF*, Congestive heart failure; *EF*, ejection fraction; *LV*, left ventricle; *LVEDP*, left ventricular end-diastolic pressure; *R*, right.

The primary treatment goal is to reduce the access flow enough to improve cardiac function while continuing to support hemodialysis therapy. Depending on the available resources and skills, flow reduction can be achieved through endovascular or surgical techniques. The ultimate goal is to reduce the arterial anastomosis to around 4 mm and access flow to approximately 1000 mL/min and minimize the risk of access thrombosis.

Pulmonary Hypertension

The pulmonary arterial pressure (PAP) is dependent on two factors: CO and pulmonary vascular resistance (PVR). A systolic PAP of less than 30 mm Hg is considered to be normal.

$$PAP = CO \times PVR$$

Pulmonary hypertension is considered to be mild when PAP is between 30 and 45 mm Hg, moderate when PAP is between 45 and 65 mm Hg, and severe when PAP is >65 mm Hg. The prevalence of pulmonary hypertension in the hemodialysis population is believed to be around 40%. A high access flow will most certainly contribute to high CO, contributing significantly to the development of pulmonary hypertension. Associated primary lung disease such as chronic obstructive pulmonary disease and diastolic heart failure will contribute to chronic vasoconstriction in the pulmonary vascular bed, accentuating the problem.

Treatment of pulmonary hypertension should be directed toward reducing the access blood and flow and, in turn, the CO.

Venous Hypertension

Vascular access is a closed circuit that starts at the heart and ends at the heart. Venous outflow obstruction of the access circuit with a patent arterial anastomosis can lead to venous hypertension. The development of central venous stenosis is the main reason for high venous pressures. Central venous stenosis is discussed in more detail in Chapter 17, but it primarily develops when a patient receives multiple central vein catheters (CVCs) or has a cardiac implantable electronic device (CIED) on the ipsilateral side as the vascular access. The degree of central vein stenosis will dictate the clinical manifestations. Exposure to multiple CVCs or prolonged exposure to CVC, leads to endothelial injury, which heals with fibrosis with a resultant central vein stenosis. The incidence of stenosis is fourfold higher when the CVC is placed in the subclavian vein compared to internal jugular vein. With CIEDs, two-thirds of patients develop subclinical central vein stenosis. If a vascular access is placed on the ipsilateral side as the CIED, the central vein stenosis gets unmasked due to the high access flows.

The clinical manifestations will depend on the degree of central vein obstruction (stenosis). Mild to moderate stenosis will present with unilateral upper extremity edema, prolonged bleeding (>30 minutes) post needle withdrawal, heaviness of the upper extremity, unilateral breast edema, and accessory veins in the upper arm and pectoral region. With severe stenosis, usually associated with total central vein occlusion, symptoms such as facial edema, shortness of breath, exophthalmos, hoarse voice, breast edema, and engorged veins in the pectoral/neck region are fairly common.

Diagnosis is confirmed with a central venogram. Treatment involves treating the central stenosis and simultaneously addressing a high-flow fistula. Usually, an endovascular approach is the preferred treatment of choice. However, central venous lesions tend to have an elastic recoil and frequently recur, necessitating close monitoring and frequent interventions. Stent placement does not necessarily increase the duration of patency, as in-stent stenosis is a common complication. The use of drug-coated balloons for central vein angioplasty has not been widely studied, although it seems a promising therapy for the future. Surgical treatment for central vein stenosis may be needed but requires a skilled surgeon, an excellent anesthesia team, and resources to manage a complex and high-risk operation. Resection of the first rib and/or the medial third segment of the clavicle to relieve thoracic outlet obstruction and surgically creating a bypass conduit are some of the available options. A recent advancement includes using an inside–out endovascular technique to create a new track to bypass a totally occluded central vein on the right side.

Posttransplant Hyperdynamic Circulation

Once a patient receives a successful allograft, the clinical question that remains controversial is how best to handle a functional vascular access. Besides being an aesthetic aspect from a patient perspective, a functioning vascular access results in hyperdynamic circulation and a risk factor for future cardiac decompensation. A mature fistula results in hypertrophy of the feeding artery along with an increase in the CO. Purely from an aesthetic perspective, ligating an access is a simple solution. However, the hypertrophied feeding artery and its high flows can lead to arm swelling, and because of the relatively sluggish venous return post ligation, the risk of developing arterial thrombosis remains high, compromising distal extremity circulation and limb ischemia.

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19

Infectious Complications From Vascular Access

MOLLY FISHER, DO • MICHELE H. MOKRZYCKI, MD

Overview of Vascular Access Infections

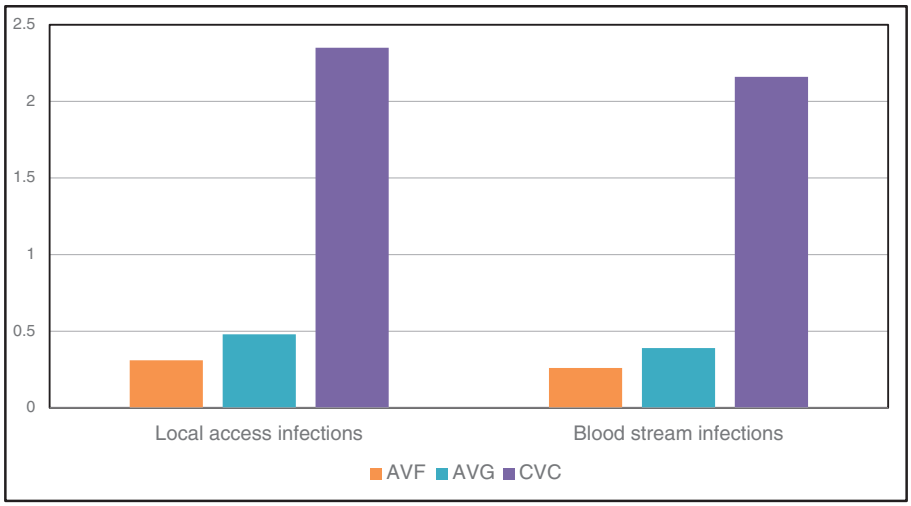
In 2017, in the United States, there were more than 468,000 prevalent and 108,000 incident hemodialysis patients. Provision of hemodialysis requires direct access to a large vein to enable venous blood to be pumped through the circuit, including the hemodialysis filter, which is then returned back to the patient via a conduit into the draining vein. Available options for vascular access include a dual-lumen central venous catheter (CVC) (nontunneled or tunneled) or via needle cannulation of an arteriovenous graft (AVG) or arteriovenous fistula (AVF). Nontunneled CVCs are often inserted for immediate short-term vascular access when hemodialysis is urgent. Tunneled CVCs have a subcutaneous cuff that becomes embedded into the subcutaneous tissue. It has been hypothesized that the cuff may reduce infection by inhibiting bacterial migration into the tunnel; however, evidence for this is lacking in the published literature. The presence of an indwelling CVC or repeated needle cannulation of an arteriovenous (AV) access may result in local infections (cellulitis and/or infections of the subcutaneous tunnel) and/or bloodstream infections (BSIs). Of the available types of hemodialysis vascular access, CVCs are the least preferred due to their associated risk of infections, higher hospitalization rate, and excess mortality when compared to AV accesses. Although prevalent CVC use has declined over the past 10 years, accounting for 18.9% of vascular accesses in 2017, there has been little change in their use in incident hemodialysis patients, and CVCs remain the vascular access used in 80% of newly starting hemodialysis patients.

Hemodialysis Catheter-Related Infections

Catheter-Related Blood Stream Infection Rate

CVCs account for an overwhelming majority of hemodialysis vascular access-related infections. In the United States, outpatient hemodialysis facilities report health-care-associated infection data to the Centers for Disease Control and Prevention (CDC) using an Internet-based surveillance system, the National Healthcare Safety Network (NHSN). The dialysis events reported to the NHSN include (1) positive blood cultures, (2) intravenous (IV) antibiotic starts, and (3) pus, redness, or increased swelling at the vascular access site, which would indicate a local infection. The NHSN data have been used by the Centers for Medicare and Medicaid Services (CMS) as part of the End-Stage Renal Disease Quality Incentive Program (ESRD QIP) since 2012 to assess facility performance. In the most recent NHSN 2014 surveillance report, which included data from over 6000 hemodialysis facilities, the rates of BSI were higher in patients who had a CVC compared with patients with other vascular access types. For CVC-dependent patients, the BSI rate was 2.16 per 100 patient months, whereas, in patients with AVFs and AVGs, the BSI rate was 0.26 and 0.39 per 100 patient-months, respectively (Fig. 19.1). Although hemodialysis CVCs represented 19% of patient months reported, they accounted for 69% of all access-reported BSIs. Similar results were reported in a single-center study by Al-Solaiman et al., who reported that the rate of catheter-related BSI (CRBSI) was 3.17 per 1000 catheter-days, whereas the rate was 0.33 and 0.14 per 1000 access-days for AVG and AVF infections, respectively. Patients dialyzing with a CVC have a significantly higher risk of both fatal (2.12; 95% confidence interval [CI], 1.79–2.52) and nonfatal (4.66; 95% CI, 2.63–8.26) infections compared with patients using AVFs. This was observed in a study by Ravani et al., who performed a meta-analysis of 62 studies, which included over 500,000 participants.

The association of BSI risk with vascular access type was also reported in an incident older hemodialysis population (≥67 years). In a cohort of 2352 Medicare ESRD beneficiaries, Kazakova and others from the CDC observed that 17.2% of patient-initiated hemodialysis with an AVF, and 79.5% of patients started with a CVC over a 2-year period. Those starting hemodialysis with an AVF had a 61% lower risk for BSI compared with CVC-dependent patients (hazard ratio [HR], 0.39; 95% CI, 0.28–0.54) in an adjusted analysis.



• **Fig. 19.1** Rate of access infections per 100 patient-months by vascular access type. *AVF*, Arteriovenous fistula; *AVG*, arteriovenous graft; *CVC*, central vein catheter. (Reproduced from Nguyen DB, Shugart A, Lines C, et al. National Healthcare Safety Network (NHSN) dialysis event surveillance report for 2014. *Clin J Am Soc Nephrol*. 2017;12:1139–1146.)

In a Canadian observational cohort study of 1041 patients who initiated outpatient hemodialysis therapy with a tunneled catheter between 2004 and 2012, bacteremia occurred in 9% and 11% at 1 and 2 years, respectively. These were recently published data from an observational cohort study that included over 1000 patients by Poinen et al.

Hospitalizations for Catheter-Related Blood Stream Infections

The U.S. Renal Data System (USRDS) Annual Data Report (2018) identified a total of 870,783 hospitalizations in ESRD patients and 160,002 readmissions. When analyzed according to clinical classification, the most common principal diagnosis was septicemia, accounting for nearly 81,000 admissions (9.3%) and 14,500 readmissions (8.6%). In an analysis of infection-related hospitalization published in 2005 by Allon and colleagues for the Hemodialysis (HEMO) Study Group, only 21% of infection-related hospitalizations were access related. However, in the HEMO study the proportion of patients with CVC dependence was low, only 7.6%. Despite their relatively low prevalence, CVCs disproportionally accounted for 32% of patients requiring hospitalization for infection. Whereas, in a study which included only CVC-dependent patients (n = 268), Al-Solaiman reported that the majority of infection-related hospitalizations were access-related infections (77%). Similarly, in the study by Poinen et al., bacteremia was responsible for 72% of all CVC-related hospitalizations. On average, hospitalization was needed in ~30% of CRBSI episodes.

The relationship between vascular access type and hospitalization rates in an incident cohort of older hemodialysis patients was recently evaluated by Kazakova and colleagues from the CDC. They observed that the risk of hospitalizations for BSI was 61% lower among AVF patients when compared to those with a CVC (HR, 0.39; 95% CI, 0.28–0.54). Hospitalization rates are 50%–70% higher in CVC-dependent hemodialysis patients than in those patients with an AVG or AVF. Fortunately, between 2007 and 2016, the rate of hospitalization for hemodialysis vascular access infections in the United States declined by 56%, from 0.26 to 0.13 hospitalizations per patient year; however, further improvement is needed.

Mortality Associated with Central Venous Catheters

Patients receiving hemodialysis with a CVC have a higher all-cause mortality compared to those with an AV access. In a large meta-analysis by Ravani et al., CVC-dependent patients were reported to have a >50% higher risk for all-cause mortality (relative risk [RR], 1.53; 95% CI, 1.41–1.67) when compared to patients dialyzing with an AVF. Historically, the CVC was implicated as having a major role in patient mortality, presumably due to fatal infections. However, more recent studies have shed light on this relationship. In an interesting study of over 115,000 incident hemodialysis patients who were >67 years old, Brown et al. compared mortality in three groups of patients: those initiating hemodialysis with an AVF, those dialyzing with a CVC after an AVF was attempted, and those dialyzing with a CVC who never had an AVF attempted. Patients initiating hemodialysis with a CVC after failed AVF placement had significantly lower mortality rates than the AVF-naïve CVC-dependent patients (HR, 0.66; 95% CI, 0.64–0.69). Similar findings were reported in a retrospective study by Quinn et al., which included 2300 incident Canadian hemodialysis patients who were ≥18 years of age. A significantly lower mortality was observed in patients <65 years old (40% lower) and in patients ≥65 years (51% lower only in the first 2 years of hemodialysis) for whom a predialysis AVF was attempted, compared with those who did not. Patients who had undergone a predialysis AVF attempt were more likely to receive predialysis care and had higher body mass index, higher values for serum albumin, calcium, and blood hemoglobin, and a lower estimated glomerular

filtration rate at dialysis initiation. They were also less likely to have congestive heart failure or start dialysis in the hospital or intensive care unit (ICU). In this study, a very small number of deaths, 14/617 (2.3%), were considered access related, and of the 14 patient deaths, majority (71.4%) were attributed to CVC complications. These data suggest that underlying patient factors and other determinants of patient selection for predialysis AVF surgery contribute to the excess mortality associated with CVC dependence.

Although CVC-dependent patients have a 1.5–2-fold higher risk of death caused by infection in comparison to those with AVGs and AVFs, the reported fatal infection incidence in episodes of CRBSI is relatively low. In an analysis of data from the HEMO study population published in 2005, Allon et al. reported that 3.8% of CVC-dependent patients hospitalized with first access–related infection died. In a prospective controlled study of 223 incident CVC-dependent hemodialysis patients presenting with their first episode of CRBSI, 4% of all patients died of sepsis within 90 days. In this 2006 study, Mokrzycki et al. observed that, over a 2-year study period, the use of a designated infection manager in outpatient hemodialysis facilities was associated with significantly lower risk of fatal infections. In the preintervention observation period, the incidence of sepsis-related death after CRBSI was 5% in all hemodialysis facilities. Thereafter, in facilities without an infection manager, the incidence of septic death remained similar, 6%. However, those facilities that assigned an infection manager reported 0 deaths due to sepsis ($p < 0.02$). In another study, Mokrzycki et al. observed that episodes of CRBSI presenting with local CVC erythema and/or purulence, indicative of an exit or tunnel infection, were associated with a significantly higher rate of fatal infection (HR, 7; $p < 0.001$). In a Canadian study by Poinen et al., only 0.5% of deaths were directly attributable to sepsis associated with CRBSI at 1 year in a cohort of incident CVC-dependent hemodialysis patients.

Risk Factors for Catheter Infections

One of the strongest factors predictive of BSI risk in CVC-dependent hemodialysis patients is a previous episode of BSI. In the Danish National Registry, of the 479 patients who initiated hemodialysis with a tunneled CVC between 2010 and 2014, 68.4% had one episode of BSI, 21.8% had a second episode, and 9.7% had three or more BSI episodes. This may be due to a variety of factors, including the overall hygiene of the patient, lapses in attention to self-catheter care, CVC colonization, and the presence of *Staphylococcus aureus* colonization. In the U.S. hemodialysis population the prevalence of intranasal and extranasal *S. aureus* colonization is between 30% and 57%, and the pooled prevalence of methicillin-resistant *S. aureus* (MRSA) colonization is 7.2%. In a meta-analysis of 38 studies including over 4790 hemodialysis patients, Zachariodakis et al. reported that MRSA colonized hemodialysis patients had an 11.5-fold higher risk of developing an MRSA infection than those who were not colonized.

Older patient age was found to be inversely related to CRBSI risk in two recent studies. The first, by Murea et al., reported a 67% lower risk of CRBSI in elderly patients ($n = 90$; mean age, 81.3 years) compared to their younger counterparts ($n = 374$; mean age, 54.8 years). In this study, Murea et al. observed CRBSI rates of 0.55 vs. 1.97 per 100 CVC-days in the elderly and nonelderly patients, respectively (HR, 0.33; 95% CI, 0.20–0.55). Poinen also reported a lower risk of CVC complications in patients who were ≥70 years old.

Immunocompromised patients have a higher risk of CRBSI (RR, 1.6; 95% CI, 1.0–2.5). In a small study by Marr et al., of the 23 immunocompromised patients, 15 were receiving long-term corticosteroids, 5 were human immunodeficiency virus (HIV)-positive, and 3 had a malignancy. HIV has not been shown to be a significant risk factor for CRBSI in two larger controlled studies, but HIV is associated with a higher risk of gram-negative (fivefold), fungal (sevenfold), and polymicrobial infections when compared to non-HIV hemodialysis patients with CRBSI.

IV iron administration and CRBSI risk are dependent upon the intensity of dosing and iron indices. Li and colleagues reported a high risk of infection-related morbidity and mortality among more intensive IV iron strategies. These findings were based on clinical data obtained from a large U.S. dialysis provider linked to Medicare data in a cohort of over 13,000 incident in-center hemodialysis patients aged ≥65 years who survived >90 days. In contrast, in a recent secondary analysis of the 2019 Proactive IV Iron Therapy in Haemodialysis Patients (PIVOTAL) trial, which was a large randomized controlled trial of IV iron in over 2000 hemodialysis patients, Macdougall found no significant difference in infection rates between the high-dose (proactive) and low-dose (reactive) IV iron sucrose groups. Patients with a CVC had a higher incidence of any infection, hospitalization for infection, and fatal infection when compared to the AVF patients, but IV iron dosing had no effect on these outcomes. One explanation for the differences in outcome between the two studies is that the highest dose used in the proactive iron strategy arm of the PIVOTAL study was less intensive than all five iron strategies evaluated in the study by Li (median monthly iron dose, 264mg vs. 299–334mg).

The type of hemodialysis CVC design, venous site of insertion, and duration of use are additional factors associated with CRBSI risk. Tunneled CVCs have a subcutaneous cuff that serves as a mechanical anchor and may be used for both short- and long-term use. Nontunneled CVCs are often inserted for immediate short-term vascular access when hemodialysis is urgent, lack the subcutaneous cuff, and have been associated with higher infectious risks in several studies. In the NHSN report from 2006, Klevens et al. reported that mean BSI in CVC-dependent patients was higher in nontunneled CVCs compared to tunneled CVCs (access-related BSI: nontunneled CVC, 17.8 vs. tunneled CVC, 3.1 per 1000 patient-months). Similarly, in a 2018 retrospective study of the Danish Registry including 479 tunneled and 782 nontunneled CVC–dependent incident hemodialysis

patients, Nelveg-Kristensen and colleagues observed a higher rate of initial BSI associated with nontunneled CVCs (HR, 6.87; 95% CI, 5.57–8.48) than with tunneled CVCs (HR, 2.25; 95% CI, 1.74–2.90), when compared to the reference group of peritoneal dialysis patients. The presence of a nontunneled CVC was also a significant risk factor for subsequent BSI and post-BSI mortality. In a retrospective study from the Netherlands, which included 2746 CVCs and a total of 145,008 catheter-days, Van Oevelen and colleagues compared tunneled CVCs, precurved nontunneled CVCs, and straight nontunneled CVCs. The incidence of systemic infection was lowest in the patients with tunneled CVCs. Reported systemic infection rates per 1000 catheter days were as follows: tunneled CVC internal jugular (IJ) vein, 0.66; nontunneled CVC precurved IJ vein, 0.84; and nontunneled CVC straight IJ vein, 1.56. The authors speculate that a higher infection risk with nontunneled CVC straight design may be due to the upwardly directed exit site in the IJ vein, as compared with a precurved nontunneled CVC design. The highest systemic infection rate was associated with femoral nontunneled CVCs, 2.44 per 1000 catheter-days. Similarly, Oliver et al. reported a threefold higher risk in bacteremia associated with femoral vein nontunneled CVCs compared to IJ and subclavian vein nontunneled CVCs (RR, 3.1; 95% CI, 1.1–8.5) in 211 hemodialysis patients. Although the anatomical site of CVC insertion is a risk factor for nontunneled CVCs, it is not a risk for tunneled CVCs in hemodialysis patients. Maya and Allon reported similar infection-free survival in 27 hemodialysis patients receiving a femoral tunneled CVC compared to those with IJ tunneled CVCs. A recent larger study by Guillermo-Corpus et al., which included 144 femoral vein tunneled CVCs, and 622 jugular or subclavian vein tunneled CVCs, reported similar infection rates (0.25 per 1000 catheter-days) between the upper and lower tunneled CVCs. The duration of tunneled CVC dependence has been reported to be a significant risk factor for CRBSI. In a study of 472 incident CVC patients, Shingarev et al. observed that the CRBSI rate more than doubled from 35% at 3 months to 79% at 12 months. In this study, CRBSI was not associated with patient age, race, sex, diabetes, heart failure, vascular disease, or site of tunneled CVC insertion.

Two recent reports shed light on the relatively novel factors associated with CRBSI risk. The first was a study reporting an inverse relationship between the percentage of CVC patients and CRBSI rate. This study, by Brown et al., was performed using data from 179 New England Dialysis outpatient facilities collected between 2015 and 2016. Facilities with $<10\%$, 10%–14.9%, 15%–19.9%, and $\geq 20\%$ CVC-dependent patients had BSI rates of 4.4, 2.2, 1.9, and 1.5 per 100 patient-months per patient group, respectively (adjusted $p < 0.001$). There was no seasonal effect difference in facility patient census or BSI difference observed in the patients with AV accesses. This surprising finding may be due to improved antiseptic technique during accessioning of the CVC by staff in hemodialysis facilities with a higher proportion of CVCs. Alternatively, one can speculate that in facilities with a higher percentage of CVCs, there may be a significant number of patients dialyzing with a CVC who would be suitable for an AV access and may be less prone to infections. The second recent report by Novosad et al. from the CDC linked a multicenter outbreak of serious gram-negative BSI (*Serratia marcescens*, $n = 21$, and *Pseudomonas aeruginosa*, $n = 12$) to contaminated fluid from the wall boxes in three hemodialysis facilities. The majority of cases occurred in patients with a CVC (50/57 cases; odds ratio [OR], 54.32; 95% CI, 12.19–∞), which was attributed to lapses in staff hand hygiene. Observations of wall box basin drains clogged with wasted dialysis effluent, and staff touching wall boxes and then proceeding to perform CVC care without performing hand hygiene were reported. Contamination due to improper antiseptic technique during medication administered during hemodialysis has also been reported to be a potential source of BSI. Grohskopf and colleagues at the CDC reported *Serratia liquefaciens* BSI ($n = 10$) linked to puncturing and pooling preservative-free epoetin alfa and contaminated reused soap in a hemodialysis unit. The authors hypothesize that *S. liquefaciens* passed from the hands of hemodialysis staff that were transiently contaminated by soap or hand lotion to the epoetin alfa, which was rectified after the cessation of pooling epoetin alfa and the switch to single-use antibacterial soaps.

Types of Catheter-Related Infections

CVC-related infections can be categorized as a local exit-site infection, tunnel infection, and/or CRBSI. Bacteria can be introduced into the bloodstream via migration from the skin by way of the CVC tunnel (extraluminal pathway) or by entry into the CVC lumen while accessing the CVC hub if there is improper handling and a break in aseptic technique (intraluminal pathway). Exit-site infections present with erythema, induration, or tenderness over the CVC exit site, whereas tunnel infections present with serous or purulent discharge expressed from the tunnel and marked tenderness over the tunnel. The rate of local access infection in CVC-dependent patients was 2.35 per 100 patient months, as reported in the NHSN 2014 report (see Fig. 19.1). In a study of CVC-dependent patients by Al-Solaiman et al., the CVC exit-site infection rate was reported to be 0.38 per 1000 catheter days and only 4.3% of cases required hospitalization. Uncomplicated exit-site infections may be treated with topical antibiotic ointment applied to the exit site or oral antibiotics. However, if the exit-site infection is associated with CRBSI, the CVC may need to be removed. CVC exit-site infection was present in ~38% of cases in one series of 226 episodes of CRBSI reported by Mokrzycki. Tunnel infections, which extend into the subcutaneous tissue, require CVC removal regardless of the presence of CRBSI, in addition to treatment with systemic antibiotics.

Metastatic infectious complications such as endocarditis, osteomyelitis, epidural abscess, and septic thrombophlebitis may occur in episodes of CRBSI (Table 19.1). Mokrzycki

TABLE 19.1 Metastatic Complications of Catheter-Related Bacteremia in People Undergoing Long-Term Hemodialysis

Complication	Frequency (%)
Endocarditis	3–34
Large atrial thrombi	Rare
Spinal epidural abscess	Rare
Septic pulmonary emboli	0.4
Septic emboli other organs (for example, the brain)	1–2
Other abscess	1.5
Septic arthritis	2–5
Osteomyelitis	1.5–15

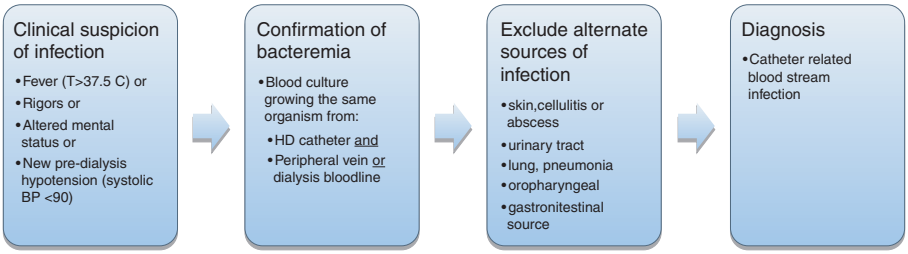
et al. reported infectious complications in an average of 7% of patients, and the risk is higher in CRBSI episodes associated with *S. aureus* (13%) in comparison to gram-negatives (3%). In a 2017 study from the Danish National Registry, including over 7200 hemodialysis patients, Chaudry et al. reported a higher incidence of endocarditis in CVC-dependent hemodialysis patients compared to those with AVFs (RR, 3.5 for nontunneled CVC vs. AVF, and RR, 2.4 for tunneled CVC vs. AVF). In this study, there was no significant difference between nontunneled CVCs and tunneled CVCs (HR, 1.40; 95% CI, 0.89–2.21). The in-hospital and 1-year mortality rates were 20% and 46%, respectively, in hemodialysis patients with endocarditis. Rarely, a large atrial septic thrombus can develop at the tip of the CVC and is associated with a high overall mortality rate of 27%, including mortality as high as 83% when associated with *Staphylococcal* CRBSI.

Diagnosis of Catheter-Related Infections

The appropriate management of CRBSI first requires a correct diagnosis to determine if the CVC is the source. The standard Infectious Disease Society of America (IDSA) definition of CRBSI from 2009 is as follows, "A definitive diagnosis of CRBSI requires that the same organism grow from at least 1 percutaneous blood sample culture and from the catheter tip, or that 2 blood samples for culture be obtained (1 from a catheter hub and 1 from a peripheral vein) that meet CRBSI criteria for quantitative blood cultures or differential time to positivity. Alternatively, 2 quantitative blood cultures of samples obtained through 2 catheter lumens, in which the colony count for the blood sample drawn through one lumen is at least three-fold greater than the colony count for the blood sample obtained from the second lumen, should be considered to indicate possible CRBSI." The relatively stringent IDSA criteria are not practical for use in most freestanding outpatient hemodialysis facilities without access to referral labs to perform quantitative and qualitative blood culture testing and have not been validated in hemodialysis patients. Furthermore, obtaining peripheral vein cultures may be difficult in hemodialysis patients due to previous vein injury and the desire to preserve venous anatomy for a future AV vascular access.

In 2018, the Kidney Health Initiative's Catheter End Points Workgroup, which included experts in infectious disease and nephrology, and representatives of the CDC and Food and Drug Administration (FDA), proposed the following revised CRBSI definition: (1) clinical suspicion of infection with fever/temperature >37.5°C, rigors, altered mental status, or new predialysis hypotension; (2) confirmation of bacteremia from blood cultures growing the same organism from the hemodialysis CVC and a peripheral vein *or dialysis bloodline*; and (3) exclusion of any alternate sources of infection (Fig. 19.2). Potential sources of BSI, other than the CVC, in this population may include pneumonia, skin infection such as cellulitis/abscess/gangrene, an abandoned AVG infection, pharyngitis or dental abscess, a primary urinary source, and a gastrointestinal infection.

The presenting signs and symptoms of CRBSI in hemodialysis patients may be atypical and may or may not include fever with or without rigors, altered mental status, and unexplained hypotension. Hemodialysis patients have a lower basal temperature; therefore, fever should be defined as a temperature of ≥37.5°C, rather than >38°C used in nondialysis patients. In a prospective study of 226 cases of CRBSI in incident hemodialysis patients, Mokrzycki observed that the maximum temperature at presentation was



• **Fig. 19.2** Proposed criteria for the diagnosis of catheter-related bloodstream infection by the Kidney Health Initiative Dialysis Catheter Endpoints Workgroup. *BP*, Blood pressure; *HD*, hemodialysis. (Reproduced from: Allon M, Brouwer-Maier DJ, Abreo K, et al. Recommended clinical trial end points for dialysis CVC. *Clin J Am Soc Nephrol*. 2018;13(3): 495–500.)

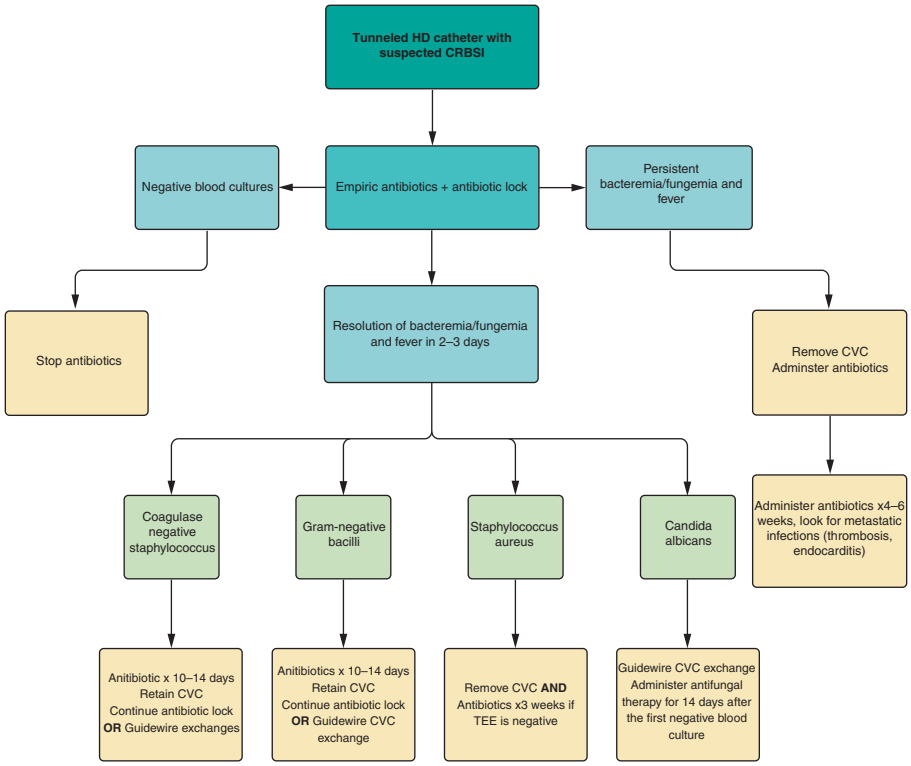
between 37.5°C and 37.9°C. Al-Solaiman et al. reported the presenting symptoms and clinical management date of 184 cases of "probable" CRBSI in an outpatient hemodialysis cohort. Fever was present in only 47% of CRBSI episodes, and the likelihood of fever at presentation was higher with *S. aureus* CRBSI (77%) as compared to gram-negative rods (46%), *Staphylococcus epidermidis* (33%), and *Enterococcus* (23%). Approximately 20% of patients in this series of "probable" CRBSI presented without fever or rigors and instead presented with more nonspecific symptoms, which included malaise, hypotension, altered mental status, and exit-site purulence.

When CRBSI is suspected, it is highly recommended that blood cultures be collected prior to the administration of antibiotics. Obtaining blood cultures after the initiation of empirical treatment reduces sensitivity by approximately 50% when pre-antimicrobial cultures are positive. Potential sites for obtaining blood cultures during hemodialysis include a peripheral vein, drawing a sample of blood from the hemodialysis circuit, or from either the arterial and venous CVC hubs. In a study evaluating blood culture acquisition from various sites during hemodialysis, concurrent blood cultures from the hemodialysis circuit and the venous CVC hub outperformed all other combinations for diagnosing CRBSI, with a sensitivity of 93% and specificity of 97%.

Antibiotic Management of Catheter-Related Blood Stream Infections

Gram-positive bacteria are the most common microbiologic isolates in CRBSI: *S. aureus* (31%), *S. epidermidis* (15.6%), *Staphylococcus coagulase* negative (9.7%), and *Enterococcus fecalis* (4.9%). Up to 39% of all *S. aureus* isolates tested in the 2014 NHSN report were methicillin resistant. Therefore, it is recommended that initial empiric treatment include broad-spectrum antibiotic coverage for MRSA and gram-negative infections until the identification and sensitivity of the final isolate are known. *S. aureus* is associated with a significantly higher rate of treatment failure and serious metastatic infections.

The recommended duration of antibiotic therapy depends upon the microbiologic isolate, the severity of the clinical presentation, response to treatment, and the presence of metastatic infectious complications. The most recent IDSA Guidelines for the diagnosis and management of intravascular CVC-related infections recognized the unique problem of CRBSI associated with hemodialysis and included a section pertaining specifically to management (Fig. 19.3). Most episodes of uncomplicated non–*S. aureus*, gram-negative, and *Candida albicans* CRBSI are treated with a 2-week course of antibiotics or antifungal agents after the first negative blood culture. A minimum of 3 weeks of antibiotic therapy is recommended for *S. aureus* CRBSI. In



• **Fig. 19.3** Catheter-related bloodstream infection *(CRBSI)* among patients who are undergoing hemodialysis *(HD)* with tunneled CVC. *CVC*, Central venous catheter; *TEE*, transesophageal echocardiograph. (Reproduced from Mermel LA, Allon M, Bouza E, et al. Clinical Practice Guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America Clinical Infectious Diseases. *Clin Infect Dis*. 2009;49:1–45.)

cases of CRBSI complicated by metastatic infection such as endocarditis or osteomyelitis, an extended 4–6-week course of antibiotic therapy is advised.

Catheter Management in Catheter-Related Blood Stream Infections

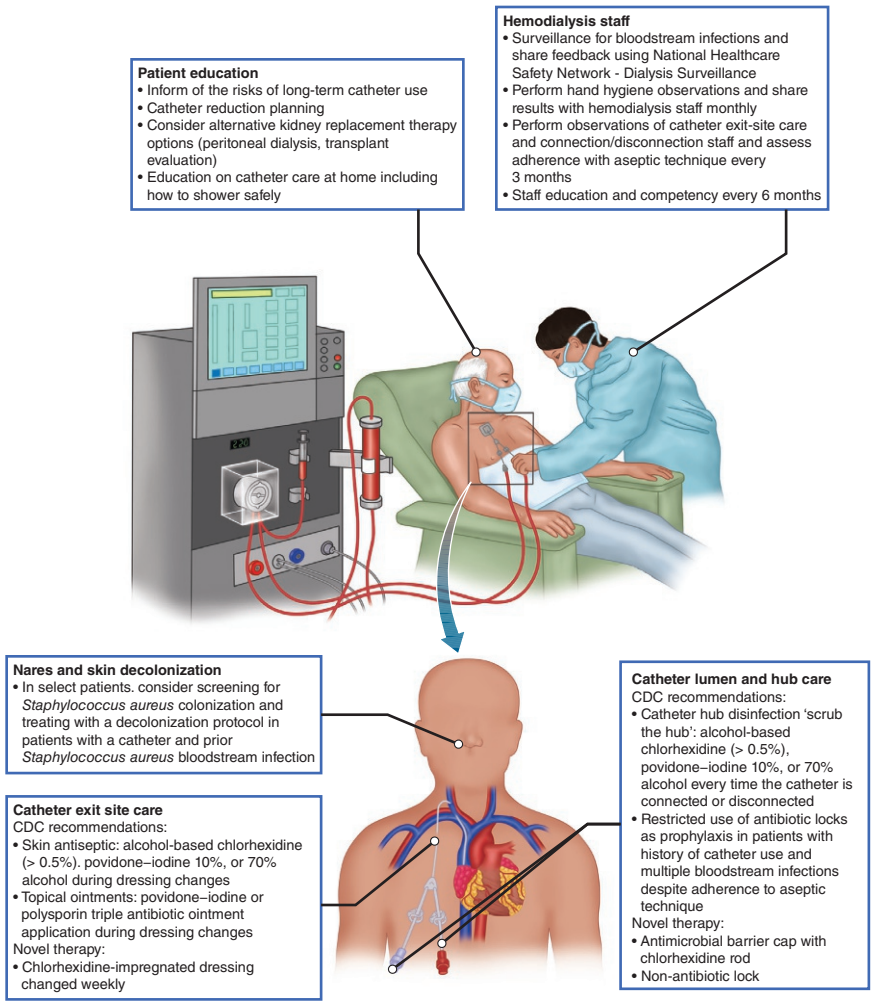
Although systemic antibiotics treat the bacteremia, they are insufficient to eradicate bacteria embedded in the biofilm, and the management strategy of CVC salvage with systemic antibiotics alone is associated with low rates of clinical cure. In addition to systemic therapy, options for CVC management, include (1) immediate removal with placement of a nontunneled CVC for dialysis until the bacteremia clears, or (2) replacement of the infected CVC via exchange over a guidewire, or (3) use of an antibiotic lock in the infected CVC. Immediate CVC removal is recommended in the setting of severe sepsis, hemodynamic instability, the presence of a metastatic infection, persistent fever after 48–72 hours of antibiotic initiation, or when infection is due to difficult to cure pathogens such as *S. aureus*, *Pseudomonas*, *C. albicans*, or multidrug-resistant organisms (see Fig. 19.3). Delayed exchange of the CVC over a guidewire for a new CVC can be considered 2–3 days after the initiation of antibiotics and resolution of fever in patients who do not meet the previous criteria for immediate CVC removal. This approach has been associated with high cure rates similar to CVC removal in select patients and has the advantage of negating the need for additional access procedures. Several prospective observational studies reported no difference between delayed reinsertion of CVC and guidewire exchange in cases of uncomplicated CRBSI. In 2017, Saleh and colleagues performed a randomized control trial in 678 hemodialysis patients with CRBSI without severe sepsis and reported no difference in outcomes between the two CVC management strategies. It is important to note that CVCs were removed for all episodes of severe sepsis and in cases when patients did not improve after guidewire exchange.

One final approach that may be considered is the use of catheter retention by instilling a concentrated antibiotic solution in the CVC lumen, known as a therapeutic antibiotic lock. Antibiotic lock is used in addition to systemic antibiotics. This approach aids in sterilizing biofilms that frequently adhere to the CVC lumen and sparing the need for CVC removal. This strategy may be particularly useful in patients with limited vascular access, allowing for salvage of the CVC. Nine prospective observational studies demonstrated a cumulative cure rate of 76% using this approach, although the success was highly dependent on the organism. Gram-negative infections and *S. epidermidis* infections had significantly higher rates of cure using this approach (75%–100%) compared to *S. aureus* infections (40%–55%). A meta-analysis on the management of CRBSI in hemodialysis was performed by Aslam et al. in 2014. In this study, outcomes associated with CVC antibiotic lock were similar to CVC guidewire exchange for hemodialysis CRBSI, and both CVC management strategies were superior to CVC salvage with systemic antibiotics alone. Among *S. aureus* infections, CVC guidewire exchange was associated with a higher cure proportion than CVC salvage with systemic antibiotics alone (OR, 3.33; 95% CI, 1.17–9.46) or antibiotic lock solution (OR, 4.72; 95% CI, 1.79–12.46).

Prevention of Catheter-Related Infections

The most obvious strategy to reduce CRBSI is CVC avoidance. Successful strategies to decrease CVC use include early nephrology referral, creation of multidisciplinary teams, use of vascular access coordinators to provide education to patients, use of early cannulation of AVG, and urgent-start peritoneal dialysis. Further reduction in CVC utilization is critical to improving infectious outcomes in hemodialysis patients. In an effort to promote CVC reduction in incident hemodialysis patients, CMS identified the long-term CVC rate (>90 days) and the standardized AVF rate as the two ESRD QIP vascular access clinical measures to be reported by U.S. outpatient hemodialysis facilities.

In addition to CVC reduction, implementation of strict antiseptic techniques and attention to CVC care are important tools for reducing vascular access infections. The core interventions for hemodialysis CVC care, identified by the CDC, have been proven to be effective in reducing CVC-related BSIs and hospitalizations for sepsis. CDC core interventions include active patient engagement, staff education about appropriate CVC care, attention to proper CVC exit site and hub disinfection using recommended antiseptic agents, and application of topical ointments during dressing changes (Fig. 19.4). Despite this guidance and available data, hemodialysis CVC BSIs continue to occur at unacceptably high rates, possibly due to lapses in adherence to strict aseptic techniques or additional factors not addressed by the CDC's core interventions. In an effort to further engage nephrologists, the CDC has contracted with the American Society of Nephrology, forming the Nephrologists Transforming Dialysis Safety (NTDS) Committee to improve infectious outcomes and patient safety in the hemodialysis setting. One of the components of the CDC's core interventions is the recommendation that observations of vascular access care and CVC accessing by the hemodialysis staff be performed quarterly. Printable CVC checklists are available on the CDC's website to assess staff adherence to recommended aseptic techniques when connecting, disconnecting CVCs, and during dressing changes. The NTDS's Vascular Access Workgroup, together with the CDC, has developed an electronic version of the Catheter Checklist. This web-based electronic tool also contains educational videos for patients, thereby addressing another one of the CDC's core interventions, that of providing patient education and increasing patient engagement. These videos include the following topics: (1) the importance of hand hygiene, (2) CRBSI, (3) proper antiseptic techniques to prevent infection, and (4) information about the "clean hands count" campaign for dialysis. The results of a multicenter pilot study assessing the electronic Catheter Checklist should be available soon.



• **Fig. 19.4** Strategies for the prevention of catheter-related bloodstream infection in hemodialysis patients. *CDC*, Centers for Disease Control and Prevention. (Reproduced from Fisher M, Golestaneh L, Allon M, Abreo K, Mokrzycki MH. Prevention of bloodstream infections in patients undergoing hemodialysis. *Clin J Am Soc Nephrol*. 2020;15:132–151.)

Catheter Exit-Site Care

Routine exit-site care performed by hemodialysis staff at each session includes use of an antiseptic agent, allowing for recommended dry time. The preferred agent is alcohol-based chlorhexidine (> 0.5%), which has shown to be superior to povidone-iodine for CRBSI prevention in a large, randomized control trial by Olivier and colleagues. Alternative acceptable agents for patients allergic to chlorhexidine include either povidone-iodine 10% or 70% alcohol. The application of a topical antimicrobial ointment to the CVC exit site is recommended by the CDC (Table 19.2). Approved ointments are polysporin triple antibiotic ointment (bacitracin/gramicidin/polymyxin B) or povidone iodine ointment and have been associated with a 75%–93% reduction in CRBSI. Polysporin ointment was also associated with lower mortality and, in a 6-year follow-up study, was not associated with emergence of resistant microbiologic isolates. In the United States, the available polysporin ointment contains bacitracin/zinc/polymyxin B but has not been rigorously studied for CRBSI prevention. Confirming CVC-ointment compatibility before use is mandatory, and a chart is available on the CDC's website. Alternative novel therapies for CVC exit site include the use of a chlorhexidine sponge or dressing. Chlorhexidine dressings have been shown to reduce CRBSI by 50%–70% and may be changed weekly. The immediate cost of a weekly chlorhexidine dressing is twice that of dry gauzed dressings; however, upfront costs may be recouped by reductions in hospital expenditures associated with lower CRBSI episodes. Chlorhexidine is a nonantibiotic antimicrobial agent; therefore, the risk for selection of resistant organisms is low.

Patient education about CVC self-care is key to CRBSI prevention. Showering should be permitted if precautions can be taken to reduce the likelihood of introducing organisms into the catheter. The CDC recommends that the CVC exit site, hub, and connecting

device be protected with an impermeable cover during the shower. There is insufficient evidence to determine if after-shower exit-site care or the use of catheter hub protection devices reduces CRBSI rates when compared to a no-showering policy.

Catheter Hub Care

Routine CVC hub disinfection is required each time it is accessed, preferably using an alcohol-based chlorhexidine (> 0.5%) antiseptic solution, povidone-iodine 10%, or 70% alcohol, with attention to appropriate dry times. Additional interventions, which target the CVC hub and lumen, shown to be of proven benefit for preventing CRBSI include the use of prophylactic antimicrobial locks and CVC hub devices (see Table 19.2). CVC locks used for the prevention of CRBSI are instilled into the CVC lumen between hemodialysis sessions when not in use, targeting the intraluminal route of bacteria entry, and preventing biofilm formation. Antiseptic CVC locking agents may consist of either an antibiotic or a nonantibiotic solution, in addition to an anticoagulant. The most commonly used prophylactic antibiotic containing locking solution is gentamicin, and if selected, a low-dose (0.32 mg/mL) formulation is recommended. Novel nonantibiotic antimicrobial CVC lock solutions have been developed to mitigate the risk of developing resistant organisms, a potential serious undesirable outcome when routinely using an antibiotic lock over a long period of time. Nonantibiotic locks, which have been shown to reduce CRBSI in clinical trials, include taurolidine-citrate (4%), ethanol (30%–70%), tissue plasminogen activator (used weekly), trisodium citrate (30%–47%), and sodium bicarbonate (7.5%). There are potential risks associated with various antimicrobial locking solutions, including higher risk of CVC thrombosis and dysfunction (taurolidine-citrate, trisodium citrate); headache, nausea, dizziness, hepatotoxicity, and alteration of CVC integrity (ethanol); cost (TPA); and paresthesias, cardiac and embolic complications, and death (trisodium citrate). The addition of either heparin or urokinase to taurolidine-citrate 4% locks has been shown to be associated with improved CVC patency, a 75% reduction in CRBSI, and cost-savings and is widely used in Europe. A large randomized clinical trial in hemodialysis patients in the United States reported a 72% reduction in CRBSI (abstract presented in May 2019); however, final publication of the study and FDA approval are pending in the United States. The most recent recommendation of the CDC on the use of prophylactic antimicrobial lock solutions is for their limited use in CVC-dependent patients on hemodialysis who have a history of multiple CRBSIs.

Nasal Mucosa Prophylaxis

S. aureus is the most commonly isolated pathogen in CRBSI episodes, and nasal colonization is associated with higher risk. Decolonization with intranasal mupirocin prophylaxis has been associated with a significant reduction in the incidence of *S. aureus* BSI (see Table 19.2). This approach has not been widely adopted due to concerns of microbial selection for mupirocin resistance. However, it is reasonable to consider its limited use for decolonization in patients with recurrent *S. aureus* CRBSI.

Arteriovenous Fistula-Related Infections

Vascular access-related infections occur at much lower rates in patients receiving hemodialysis with AVFs when compared to CVC. The most recent NHSN Dialysis Surveillance Report from 2014 calculated eightfold to ninefold lower rates of local infections and BSIs for AVF patients compared with CVC patients (see Fig. 19.1). The rate of local infections associated with AVFs was 0.31 per 100 patient months, and the BSI rate was 0.26 per 100 patient months. Although AVF infections are uncommon, when they occur, the likelihood of hospitalization is fairly high; approximately 48% was reported in the HEMO study and in a single-center study by Al-Solaiman et al. in 2011. In the HEMO study, of the 783 patients with first infection-related hospitalizations, the likelihood of severe outcome, including (1) death, (2) the need for ICU-level care, and (3) extended hospital stay (≥ 7 days), did not differ among CVCs (38.5%), AVGs (39.3%), and AVFs (47.6%). Patients presenting with AV access infections are less likely to present with fevers, occurring in only ~ 18% of cases.

The type of AVF cannulation technique has been shown to be associated with infection risk. The AVF cannulation techniques commonly used in clinical practice are (1) rope ladder, (2) cluster, and (3) buttonhole (Fig. 19.5). When using the rope ladder technique, the needle insertion sites are rotated and differ between consecutive dialysis sessions. The cluster technique is when the needles are placed in the same general area of the AVF. The buttonhole technique involves the establishment of two fibrous tracts from the skin surface into the AVF. After removal of the scab, the preformed tracts are repeatedly cannulated with blunt needles for each dialysis session.

Data from international randomized trials and observational studies reported a > threefold greater risk of vascular access attributable infection using the buttonhole cannulation compared to the rope ladder technique. Serious *S. aureus* BSIs, including those with metastatic complications and death, have been reported with buttonhole cannulation of AVFs. Similar findings were reported in U.S. hemodialysis patients in whom buttonhole cannulation was associated with a 2.6-fold higher risk of access-related BSI and 1.5-fold higher risk of local access site infections. The most recent Vascular Access Guidelines, updated in 2019, from the National Kidney Foundation Kidney Disease Outcome Quality Initiative, considers it reasonable to limit

TABLE 19.2 Summary of Effective Interventions for the Prevention of Catheter Bloodstream Infection in Hemodialysis Patients

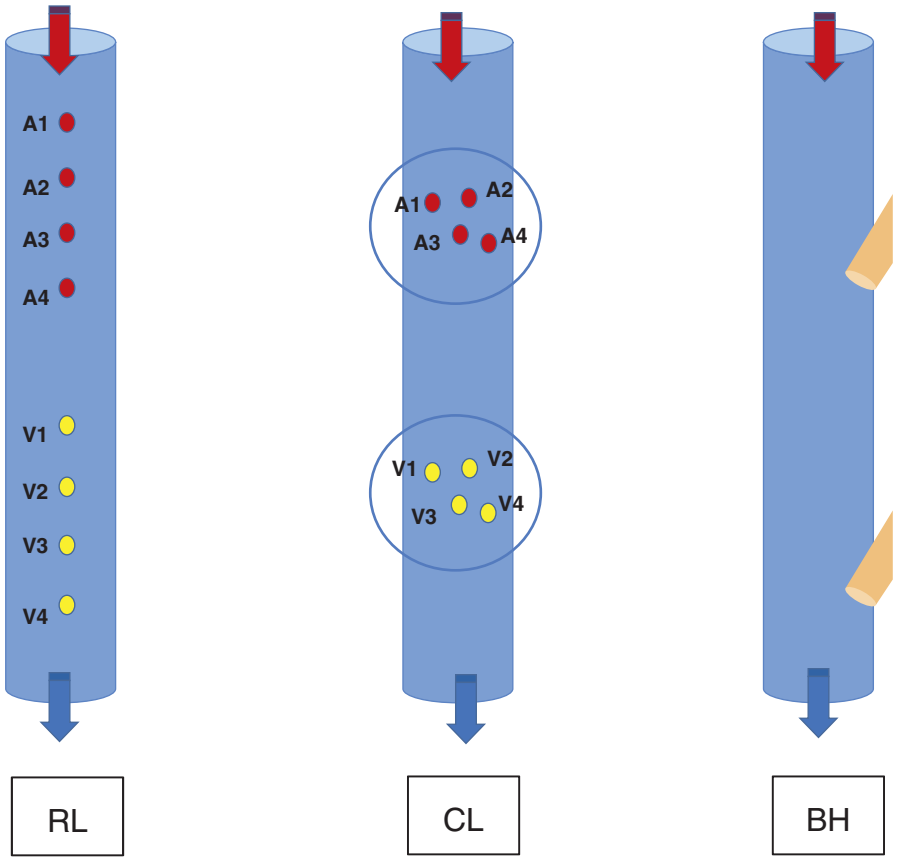
Site	Intervention	Types	Improved Outcomes	Concerns
Catheter exit site	Topical ointments	Povidone-iodine	BSI	–
		Mupirocin	*S. aureus* BSI	Microbial resistance
			BSI	
		Polysporin triple antibiotic	BSI	–
			Mortality	
	Topical dressings	Chlorhexidine dressing	BSI	Patient Cost
Catheter hub	Hub devices	Neutral valve connector	IV antibiotic start	Lack of evidence for BSI reduction and cost
		Chlorhexidine-rod cap	BSI	Cost
Catheter lumen	Antimicrobial locking solutions	Gentamicin 0.32 mg/mL + citrate 4%	BSI	Microbial resistance
			Mortality	
		Other antibiotics	BSI	Microbial Resistance
		Taurolidine 1.35%	BSI	FDA approval and cost
		+Citrate 4%	Use of thrombolytic therapy	
		+Heparin		
		Taurolidine 1.35%	BSI	No FDA approval and cost
		+Citrate 4%	CVC dysfunction	
		+Urokinase 25,000IU		
		Trisodium citrate	BSI	Safety and efficacy
		30%–46.7%		
		Tissue plasminogen activator +	BSI	Cost
		Heparin		
		Citrate 7%	BSI	No FDA approval
		+Methylene blue		
		+ Methylparabens/propylparaben		
		Ethanol 70% + heparin	BSI	Safety
		Sodium bicarbonate 7.5%–8.4%	BSI	–
			CVC loss due to BSI	
			CVC loss due to thrombosis	
Nasal mucosa	Intranasal antibiotic ointment	Mupirocin	BSI	Microbial resistance

BSI, Bloodstream infection; *CVC*, central vein catheter; *FDA*, Food and Drug Administration; *IV, intravenous*; *S. aureus*, *Staphylococcus aureus*.
Reproduced from a more detailed table which appears in Fisher M, Golestaneh L, Allon M, Abreo K, Mokrzycki MH. Prevention of bloodstream infections in patients undergoing hemodialysis. *Clin J Am Soc Nephrol*. 2020;15:132–151.

buttonhole cannulation only to AVF patients with special circumstances, such as those with AVFs with short lengths or in patients with a severe fear of sharp needles, given the associated higher risks of infection and related adverse consequences.

Arteriovenous Graft-Related Infections

As with AVFs, AVG infections may present with cellulitis, purulent discharge, swelling, and erythema. AVG-associated BSI rates of 10%–57% are reported in surgical series



• **Fig. 19.5** Commonly used arteriovenous fistula cannulation techniques for hemodialysis: rope ladder (*RL*), cluster *(CL)*, and buttonhole *(BH)*. (Reproduced from Vachharajani TJ, Wong L, Niyyar VD, Abreo KD, Mokrzycki MH. Buttonhole cannulation of arteriovenous fistulas in the United States. *Kidney360* 2020;1(4):306–313.)

and metastatic complications such as septic emboli and endocarditis may occur. In the latest 2014 NHSN Dialysis Surveillance Report, the rate of local AVG infections was 0.48 per 100 patient months, and the AVG-associated BSI rate was 0.39 per 100 patient months, still significantly lower than the CVC infection rates. In a single-center series by Al-Solaiman et al., the rate of AVG infections was 0.33 per 1000 access days, and 42.6% required hospitalization.

Early AVG infections, occurring ≤ 30 days after insertion, may be attributed to surgical revision/placement and usually are located at the surgical incision site location. Late AVG infections, which present more than 30 days post insertion, are more likely due to microbial entry during cannulation in hemodialysis or are associated with a recent fistulogram or endovascular intervention. The area of infection may span the body of the AVG. Nonfunctioning, thrombosed, abandoned AVGs may become colonized with bacteria and be a potential source of infection. The patient may present with fever and without obvious signs of infection. The diagnosis of a clinically silent graft infection requires a high index of suspicion and is frequently missed.

The vascular site of AVG insertion is an important risk for infection, which is more common with thigh AVGs as compared with upper extremity AVGs. Furthermore, thigh AVGs are associated with a higher rate of gram-negative infections (31%) and metastatic complications (15%), whereas upper extremity AVGs are associated with a predominance of gram-positive isolates (96%) and fewer metastatic complications (3%). Recently, early cannulation of AVGs has allowed for a shorter postoperative period before use for dialysis, and there appears to be no difference in infection rates between early cannulation AVGs and late cannulation AVGs, which is approximately 11% over 1 year. Endovascular treatment of AVG pseudoaneurysms using covered stent grafts may result in AVG infection in up to 35% of cases and may result in the need for surgical excision.

Prevention and Management of Arteriovenous Fistula and Arteriovenous Graft Infections

It is imperative that hemodialysis staff and patients receive adequate education and training on proper antiseptic AVF and AVG cannulation techniques. Standard of care as recommended by the CDC is as follows: (1) cleaning AV access with soap and water prior to cannulation; (2) using hand hygiene and clean gloves; (3) using an approved skin antiseptic agent, preferably with 2% chlorhexidine–70% alcohol allowing for recommended dry times; (4) avoiding

contact with the cannulation site after skin antiseptic agent is applied; (5) need for antiseptic needle cannulation and decannulation; and (6) strict antiseptic blood line connection and disconnection. Audit tools to assess hemodialysis staff competency for AV access cannulation and decannulation are available on the CDC's website.

In select AVF patients, the risk of infection associated with buttonhole cannulation may be mitigated by (1) limiting the number of cannulators; (2) establishing a strict antiseptic protocol including precannulation disinfection, preferably with 2% chlorhexidine–70% alcohol agent allowing for appropriate dry times, before and after scab removal; (3) disinfecting again with an antiseptic agent after needle removal; and (4) applying topical antibiotic mupirocin to cannulation sites.

The correct diagnosis of AV access infection requires obtaining cultures from the blood and infected AVF or AVG drainage or wound site prior to initiating antibiotic therapy. Treatment is dependent upon the severity of AV access–associated infection and the patient's future vascular access options. Antibiotics alone may be used to treat local AV access infections and cellulitis in the absence of signs of sepsis and metastatic infection. Partial AVG excision and revision have been attempted to limit morbidity in some surgical series but may require total excision if unsuccessful, occurring in approximately 25% of cases. Total AVG excision is indicated in cases of sepsis and if the entire AVG is infected. This approach requires temporary CVC bridging for ongoing hemodialysis provision and carries with it high perioperative morbidity and is associated with prolonged hospitalization stay and high readmission rates.

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SECTION 3

Peritoneal Dialysis

20

Determination of Continuous Ambulatory Peritoneal Dialysis and Automated Peritoneal Dialysis Prescriptions

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Dialysis Adequacy for Patients Receiving Peritoneal Dialysis

A major goal of dialysis therapy is to restore patients to their previous quality of life. For most patients, the objective is to eliminate uremic symptoms, such as poor appetite and fatigue. This is accomplished by prescribing a dialysis treatment of sufficient intensity to remove uremic toxins. There are numerous solutes that accumulate in kidney failure; ascribing the uremic syndrome to specific solutes is very difficult.

Self-reported patient outcomes are one key component of adequate dialysis. Improvement in common uremic symptoms (nausea, poor appetite, and fatigue) is a major goal. Many patients choose peritoneal dialysis (PD) due to the flexibility provided by the therapy. PD may provide a better quality of life for patients who work or travel. For patients on PD, "adequate" dialysis entails a regimen without unacceptable interference in their lifestyle. For example, most patients on continuous cycling peritoneal dialysis (CCPD) will not accept 14 hours of cycler time daily, nor will most continuous ambulatory peritoneal dialysis (CAPD) patients want to perform five to six manual exchanges daily. Abdominal distention is undesirable for many patients; limiting day dwell volumes may be necessary.

Normalization of serum biochemical markers is also an important goal for PD.[1,2] While hyperkalemia is rare for patients on PD, an adjustment in the prescription may be necessary in patients with elevated serum potassium. Metabolic acidosis can also be associated with adverse clinical outcomes, including muscle wasting, bone disease, and deterioration in residual kidney function (RKF). In order to improve metabolic acidosis, the dialysis prescription can be increased to obtain a normal serum bicarbonate value. Disorders in mineral metabolism also can be partially treated through dialysis. Elevated serum phosphate is associated with a higher risk of mortality. Since most phosphate is intracellular, dialytic removal of phosphate is time dependent. Therefore, prescriptions that utilize short dwell times may adversely affect phosphate removal.

The dialysis prescription can be tailored to achieve sufficient clearance of urea. Urea is a small, water-soluble molecule that quickly diffuses into dialysate. Urea itself does not appear to be overtly toxic. However, urea is easily measured, and the kinetics of urea removal is very well understood in both hemodialysis and PD. Urea removal with PD has also been examined in two randomized controlled trials (RCT) that compared different dialysis doses. While urea removal is a commonly used measure of dialysis dose, it should be emphasized that focusing solely on urea removal may lead to inattention to other measures of dialysis adequacy. Recognizing this, the most recent iteration of the International Society of Peritoneal Dialysis guidelines regarding quality of dialysis does not mandate a specific target for urea removal in a patient who is otherwise doing well clinically.

Dialytic removal of creatinine has also been used to measure the adequacy of the dose of PD. Similar to urea, creatinine is unlikely to mediate major components of the uremic syndrome. Creatinine diffuses into peritoneal dialysate more slowly than urea because creatinine is a larger molecule (113 vs. 60 Da). In addition, creatinine is secreted into the urine in the proximal tubule, in contrast to urea, which is absorbed from the urine in the terminal portion of the collecting duct. Due to those characteristics, small increases in RKF have a disproportionately greater effect to increase

creatinine clearance rather than urea clearance. Increasing creatinine clearance was the target in the intervention arm of the ADEquacy of peritoneal dialysis in MEXICO (ADEMEX) trial, an RCT comparing two different dialysis doses; however, now it is used less often in clinical practice.

The minimum amount of solute clearance necessary has not been thoroughly tested in prospective clinical trials. Observational studies provide some guidance regarding solute clearance. Studies from North America and Europe have suggested that Kt/V urea values exceeding 1.7 may be associated with better clinical outcomes. Two RCTs have examined the effect of different dialysis doses on outcomes, including mortality. One trial, performed in Hong Kong, randomly assigned groups to three different treatment targets using the Kt/V urea: 1.5–1.7, 1.7 to 2.0, and greater than 2.0.[3] There was no difference in mortality between the groups; however, patients in the low-dose group had increased hospitalizations. The second trial (ADEMEX) assigned patients receiving CAPD to two different regimens.[4] One group received four exchanges of 2 L while the high-dose group received a therapy targeted to a creatinine clearance of 60 L/week. The low-dose group had a total Kt/V urea of 1.8, while the high-dose group achieved a total Kt/V urea of 2.27. There was no significant difference in mortality or any of the other clinical endpoints.

Targeting urea (or creatinine clearance) can be useful in clinical practice. However, it is likely that other molecules contribute significantly to uremia and morbidity in patients. Larger molecules, such as β2-microglobulin, have been associated with dialysis-related amyloidosis. Protein-bound toxins, such as indoxyl sulfate have been associated with adverse clinical effects. Dialytic removal of these molecules does not correlate well with urea clearance. It is important not to sacrifice dialytic removal of these other molecules with a myopic focus on urea. For example, in some patients, rapid dialytic exchanges can achieve good urea clearance but not good clearance of sequestered molecules, protein-bound solutes, and larger molecules, such as creatinine, phosphate, and β2-microglobulin.

The Importance of Residual Kidney Function

It has been long appreciated that RKF is associated with better outcomes. For example, in the CANUSA (Canada–USA) observational study, higher RKF was associated with better survival, whereas higher peritoneal solute clearance was not. To deliver comprehensive care to patients on PD, one should employ strategies that preserve RKF. This may include therapy with antagonists of the renin-angiotensin-aldosterone system and avoidance of known nephrotoxic agents, including nonsteroidal anti-inflammatory drugs. High ultrafiltration volumes may decrease RKF if associated with a significant decrease in blood pressure. An increased number of exchanges with CAPD does not appear to reduce RKF, nor does increased ultrafiltration with icodextrin. Dialysate fluids that have a neutral pH and contain low levels of glucose degradation products (GDPs) appear to be associated with improved maintenance of RKF; however, this may come at the expense of increased extracellular volume.

RKF provides multiple benefits to the patient. One clear benefit is continuous sodium and volume removal. Patients with large urine volumes do not require large ultrafiltration volumes and, generally, can use a lower dextrose concentration during treatments. Urine volume removal is also more continuous and less likely to be associated with adverse cardiac consequences seen with faster ultrafiltration. Observational studies have suggested that urine volume is an important prognostic factor. In these trials, urine volume itself, not glomerular filtration rate, has been associated with lower mortality.

In addition to the salutary effects on volume status, it is also likely that solute removal from RKF significantly differs from that of PD. For small molecules, such as urea, dialytic removal of the toxin greatly slows as the dialysate approaches saturation; however, native kidney function allows for a more constant rate of solute removal. Some other molecules that accumulate in kidney failure are mainly intracellular, such as phosphate. Dialytic removal of these molecules is generally slow but is significantly enhanced in patients with RKF. Clearance of larger molecules and protein-bound molecules is also higher in patients with RKF. It is unknown which specific uremic toxins mediate specific pathophysiologic events, but it is likely that RKF is beneficial by removing a large number of these molecules.

Designing the Initial Prescription for Peritoneal Dialysis

Most patients will be able to perform either CAPD or automated PD (APD). Patients usually will choose the modality based on their lifestyle. For example, people who work usually prefer APD in order to avoid manual exchanges during the day. Alternatively, some patients may feel uncomfortable using a machine at night or may not want to be tethered to a machine for a long period of time. These patients may prefer CAPD. When patients begin PD, their peritoneal solute transfer rate is unknown; patients who are found to have faster peritoneal solute transfer rates may develop ultrafiltration problems and volume overload. In these cases, it may be preferred to use APD over CAPD with shorter dwell times for at least part of the day.

When starting a patient on PD, it is useful to consider the amount of RKF. Most patients initiating dialysis have significant RKF. In some patients, it may be possible to employ an incremental approach: starting with a low dose of dialysis and gradually increasing the dose if uremic symptoms persist or when RKF diminishes. There are several potential benefits to this approach. The use of low dwell volumes may improve patient's comfort and acceptance of the treatment. Low-dose treatments may allow for less total dextrose absorption during the day, providing a metabolic

• BOX 20.1 Estimating Initial Dwell Volumes in Peritoneal Dialysis[5]

A. Calculation of daily Kt/V
   K (L/day) = Dialysate Urea/Plasma Urea × Total Drain Volume (DV)
   t = 1 day
   V (L) = Volume of distribution of urea (approximately total body water)
B. Assuming equilibration of dialysate with plasma (D/P urea = 1) in a 70 kg male
   K (L/day) = 1 × DV
   t = 1 day
   V (L) = 42 L
C. Determining goal volume with goal daily Kt/V = 0.25
   DV/42 = 0.25
   DV = 0.25 × 42
   DV = 10.5 L
D. Assuming daily UF of 1 L, the volume that must be instilled to achieve this DV = 9.5 L

UF, ultrafiltration.

benefit to the patient. Furthermore, an incremental approach can allow for time during the day in which the patient does not require a dwell. These periods in which the abdomen is "dry" can be helpful to patients who wish to participate in heavy exercise or taxing work.

To estimate the required daily dwell volumes, one can start by determining the daily goal for urea clearance.[5] Although, as mentioned earlier, the goal of a weekly Kt/V urea of 1.7 is based on relatively modest data and is not an absolute imperative, that number—translating to a daily goal Kt/V urea of approximately 0.25—does provide a useful "first stab" at estimating the volumes of dialysate needed to provide high-quality PD. The equations in Box 20.1 provide guidance on back-calculating from a goal Kt/V of 0.25. This approach assumes an ideal situation in which there is equilibration of dialysate urea to plasma urea. In clinical practice, there is not complete equilibration, but most patients exceed a D/P urea ratio of 0.9 after 4 hours. This assumption may lead to the slight overestimation of Kt/V with a given prescription. However, most incident patients on PD have significant RKF, a factor that counterbalances the systemic error from that assumption. The daily kidney Kt/V can be calculated [(urine BUN/plasma BUN × urine volume) / total body water] to make the calculation more accurate in patients with RKF, where BUN is blood urea nitrogen. This value can be subtracted from 0.25 to give the goal daily dialysate Kt/V needed.

Initial Prescription for Continuous Ambulatory Peritoneal Dialysis

CAPD prescriptions usually entail one long overnight well and multiple dwells during the day. The daytime dwells usually allow for the dialysate to remain in the peritoneal space for greater than 4 hours. The kinetics of small solute movement into the dialysate can be predicted using the peritoneal equilibration test (PET). When first described by Twardowski, the PET evaluated creatinine removal at 2 and 4 hours and glucose absorption at the same time points. Patients were divided into four quartiles based on the two criteria: high, high average, low average, and low transport status. At 2 hours, the mean D/P creatinine among all patients is approximately 0.5, while the ratio approaches 0.7 at 4 hours. In general, regardless of peritoneal solute transfer rate, after 4 hours, the rate of creatinine clearance markedly slows. Due to its smaller size, removal of urea is significantly quicker than creatinine removal, and the D/P urea is greater than 0.9 after 4 hours.

If the initial prescription has three total dwells, the two daytime dwells should ideally exceed 4 hours in length to maximize small and middle molecule clearance. Shorter dwells can be done in patients exhibiting faster peritoneal solute transfer characteristics, especially if fast glucose absorption is associated with ultrafiltration problems. The process of doing a manual drain and dwell may take 30 minutes, meaning that more dwells may negatively affect the patient's quality of life. It is rare to have patients perform more than four dwells in a day.

Dwell volumes of approximately 1.25 to 1.5 L/m^2 body surface area (BSA) are well tolerated by most patients. Since intra-abdominal pressure is lowest in the recumbent state, patients on CAPD may use larger dwell volumes for the nightly dwell. Based on the calculations in Box 20.1, in a 70-kg patient, a good starting prescription would be four exchanges of 2500 mL.

Initial Prescription for Automated Peritoneal Dialysis

APD therapy includes both intermittent nocturnal PD (NIPD) and CCPD. In NIPD, the cycler performs multiple dwells and drains but leaves the abdomen dry at the end of the treatment. In CCPD, the cycler leaves the last fill prior to disconnecting the system. In addition to the total dialysate volume (Box 20.1), two other important variables to consider are cycler time and the number of dwells. The upper limit for the cycler time is largely dependent on the patient's preference. Cycler times of 10–12 hours may allow more dwells or longer dwell times; however, they are not acceptable to many patients. Most patients will need at least three cycler dwells. The cycler time will generally exceed 7 hours to accommodate dwell times of 2 hours and 20 minutes of draining/filling.

One potential pitfall in creating the APD prescription involves the dwell time. Multiple dwells of short duration (less than 2 hours) will remove significant urea and be associated with high ultrafiltration rates. However, this may come at the expense of low clearance of other important uremic molecules, such as phosphate. Multiple short drains will also increase the amount of time in which dialysate is draining or filling. Since there is no solute clearance during the periods, the overall efficiency of PD may be reduced. Furthermore, due to the occurrence of sodium "sieving," serum sodium

may increase—stimulating thirst and subsequent fluid intake—in patients using more hypertonic dialysis fluids.

Tidal PD is a variant of APD. In tidal PD, the dialysate is not fully drained after each dwell, and approximately 10%–25% of the dialysate remains in the peritoneal cavity. This technique is most often used to decrease pain associated with fills or drains. Drain pain may be due to the catheter touching the abdominal viscera after a full drain; allowing some dialysate to remain in the peritoneal cavity may prevent that physical interaction. At the end of the cycler time, all of the dialysate is drained. Although the main benefit of tidal PD is the relief of drain pain, it may increase dialysis dose since some dialysate is always in contact with the peritoneal membrane.

Increasing Dialysis Dose

The dialysis prescription may need to be changed if a patient continues to have uremic symptoms, hyperkalemia, metabolic acidosis, or hyperphosphatemia. In general, the maneuvers that will increase dialysis dose include increasing dialysis time in people with current treatment times of < 24 hours, increasing dwell volumes, and increasing dwell number. Patients receiving NIPD have a "dry" abdomen for the day; in these patients, adding a dwell during the day will significantly increase the dose of dialysis. In patients on the cycler, increasing the dwell volume is often preferred over increasing the number of cycles. Most patients are supine while on the cycler, allowing for increased dwell volumes. Furthermore, if the total cycler time is not changed and the number of dwells increases, the time of each dwell will significantly decrease, and the amount of time spent in draining and filling—during which little dialysis takes place—will increase.

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21

Peritoneal Dialysis Cyclers and Other Mechanical Devices

RAINER HIMMELE, MD, MSSH

Peritoneal dialysis (PD) cyclers were initially designed for intermittent PD to perform many frequent and short dialysis exchanges within a hospital setting. Following the introduction of continuous cycling PD (CCPD) and variations thereof, the cycler underwent modifications that allowed a broad variety of prescriptions and laid the foundation for its success as a home therapy device. Further improvements in the performance, safety, and convenience of modern cyclers have increased the utilization of automated PD (APD), which in many countries has become the predominant PD modality. Although the emphasis during the early years was mainly on optimizing hydraulics and mechanical aspects, the current development goes far beyond filling and draining the dialysate. Modern cyclers are highly integrated devices that are designed to communicate and exchange data via secure cloud services from and to the patient's home, allowing for remote patient monitoring and therapy management. Cyclers can directly interact with the caregiver by transferring patient and prescription data and actively guide the patient step by step through the treatment, enhancing the user experience and ensuring adequate use of the device. The potential characteristics of cyclers are summarized in Table 21.1.

Mechanical Aspects and Hydraulics

PD cyclers are designed to automatically deliver multiple exchanges of dialysate solution. The dialysate volume and flow are regulated by a central control unit that may include pumps, weigh scales, occluders, manifolds, electronics, and other mechanical components. An integrated heating system ensures adequate dialysate temperature. A display screen and control board allow entering patient treatment parameters and monitoring treatment success. The filling and draining of the dialysate can be performed by gravity- or pump-based systems. Mechanically, cyclers can be categorized as devices that use gravity or pumps.

Gravity-Based Cyclers

This type of cycler uses gravity to deliver the solution from the dialysate bags, through sterile tubing to a volume control unit and heater module, and into the peritoneal cavity (Fig. 21.1A). Alternatively, the dialysate bags may rest on a heating tray; from there, the solution is then transferred to the volume control module and then to the patient. In either case, the cycler ensures that the fluid is heated to body temperature and the exact prescribed volume of dialysate is delivered to the patient. After the prescribed dwell period, the spent dialysate flows by gravity through the patient line into a weigh bag, where the volume is measured to ensure complete drain and determine ultrafiltration. The dialysate is then either collected in an additionally attached drainage bag or disposed directly into the sewage. The transfer of dialysate into the sewage line can be accomplished by gravity or via a pump.

The control panel controls temperature and dwell time and monitors drain time and drainage volume. Inflow volume is determined and measured by a volume control unit or heating cabinet. Gravity cyclers often use scales for measuring drain volumes to ensure that a predetermined percentage of inflow volume is drained before a new cycle takes place and monitoring ultrafiltration. While the use of gravity-based cyclers declined due to the popularity of pump-based systems, recently, modern gravity cyclers have been developed that provide a simplistic and cost-effective alternative to pump-based systems (Fig. 21.2).

Pump-Based Cyclers

Most modern cyclers today are pump based. Various systems have been designed to actively infuse and drain dialysate. The simplest and most economical is the use of two peristaltic or roller pumps (see Fig. 21.1B). The first actively infuses warmed dialysate into the patient, and the second generates negative pressure to drain the spent dialysate.

TABLE 21.1 Potential Features of a Modern Cycler

Functionality

- Meets the needs of home, assisted care, and professional health care settings
- Performs all prescriptions (e.g., CCPD, PD Plus, tidal PD, intermittent PD, adapted PD)
- Allows adjustment of prescription parameters and limits to the individual patient needs
- Ability to vary each exchange regarding volume, dwell time, and solution used
- Allows extended treatment options to accommodate special patients:
  - High total volume of dialysate and large number of cycles with one setup
  - Maximal fill volumes (3–4 L) for large adults
  - Minimal fill volumes (100 mL) and delivery of dialysis solutions in small increments for pediatric patients
- Automatic priming of the patient line and flush-before-fill as part of the setup
- Fast and efficient warming of solutions or timer-controlled preheating
- Features optimized fill and drain logic allowing fast drainage (> 200 mL/min), intelligent end of drain detection, including established criteria to prevent overfill
- Last bag option and ability to pump effluent to either bags or drain
- Individualized user permission/user access configuration

User Interface

- Large color touchscreen control panel that is easy to read and use
- Variable voice and alarm volume or voice guidance
- User-friendly menu with easy-to-follow step-by-step instructions and video tutorials in multiple languages
- Integrated camera for real-time video assistance

Information Technology

- Comprehensive data capture and storage of all relevant patient treatment parameters
- Connectivity through Bluetooth, USB ports, WLAN, LAN with secured data communication, including a help feature with online access to cloud service
- Automatic wireless data import from scale and blood pressure monitor
- Interface and automatic data exchange with clinic management software
- Full therapy and patient data management, including prescription modeling, automatic prescription programming, administrative module, and upgradable training courses

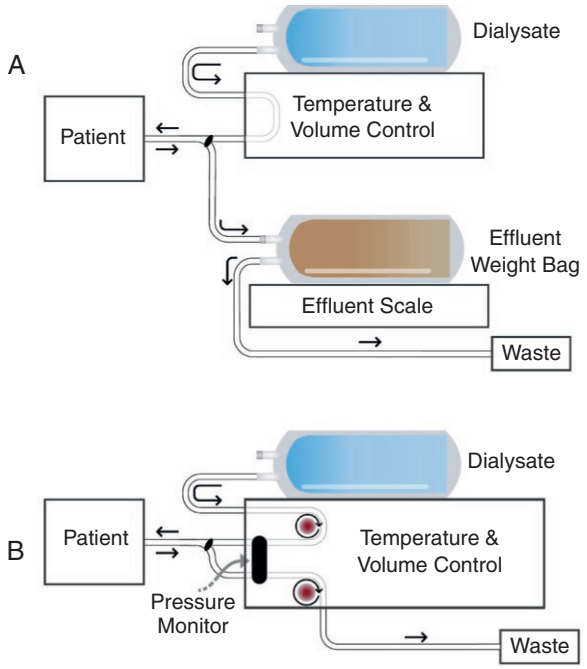
Mechanical

- Low weight hardware with custom-made travel case for ease of portability
- Small system footprint to fit in close to bed or onto average nightstand
- Stability to hold a broad range of bag sizes (up to 6 L) without tipping, and with locking wheels and nonslip feet to prevent rolling and sliding
- Able to withstand extreme temperatures with adequate performance at sea level and high altitudes
- Constructed of material that is easily disinfected with common agents and sealed outer case to prevent trapping of foreign matter and liquids from penetrating into the unit
- Silent operation with noise level < 35 dBA while running at maximum pumping speed
- 100 and 240 V AC power choices
- UL/CSA/CE approval

Disposables

- Singe-use, sterile components
- Easy and quick setup, ideally one-step loading (cassette)
- Advanced connectology with elimination of clamps
- Organizer to facilitate safe connections and disconnections and reduce contamination and infection risk

CCPD, Continuous cycling peritoneal dialysis, *LAN*, local-area network; *PD*, peritoneal dialysis; *USB*, Universal Serial Bus; *WLAN*, wireless local-area network.



• **Fig. 21.1** Flow Diagrams for Different Types of Cyclers. (A) Gravity-based cycler; (B) pump-based cycler.

A more ingenious alternative is the use of an integrated cassette design for easy setup of the cycler. The exact measurement of fluid volume flowing through the cassette can be used for volumetric control and eliminates the need for weigh scales. Current systems contain fluid chambers that serve as pumps and a series of channels for solution flow (Fig. 21.3A).

Examples of modern pump-based cycler designs are provided in Fig. 21.4.

Connectology

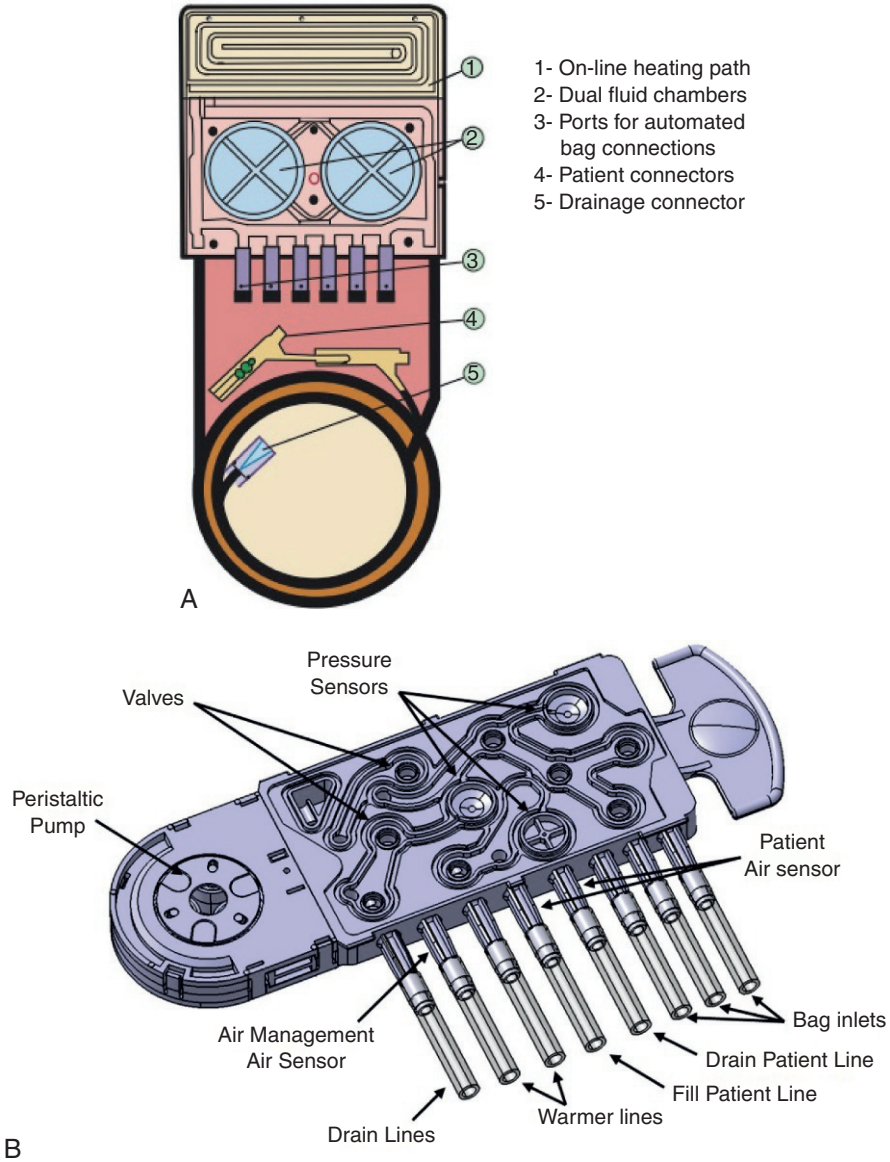
Connectors are required between the cycler tubing set, the patient's catheter, and the solution bags. Various connectors have been used, including spikes, Luer locks, and threaded male-female connectors with recessed pathways. Dialysate bags with integrated patient and drain lines add more convenience for the patient due to fewer connections as the whole disposable setup becomes simpler. Connections can be manually performed or facilitated by automated spiking (Fig. 21.5A). Automated connections use a stationary manifold and a moving tray (connection rail) to attach the bag lines to the cassette. This technology simplifies the procedure and reduces the risk of touch contamination by the patient. In addition, the cycler's connecting device may incorporate a bar-code scanner that identifies the specific solution connected to each port in the manifold by reading the printed bar code on the bag connector (Fig. 21.5B).

Upon termination of the cycling session, the patient line can be disconnected and capped using a sterile technique, external occlusion, or with connectors that automatically occlude the lumen of the tubing with a pin to prevent leakage of dialysate or contamination (Fig. 21.6).

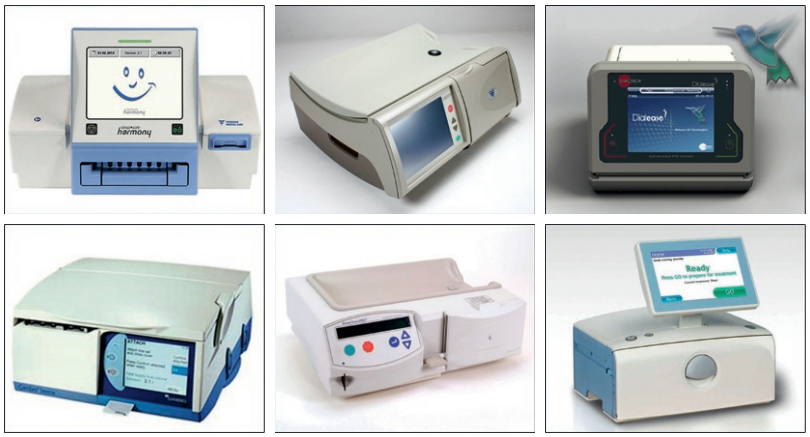
Information Technology and Connectivity

Connectivity features in modern cyclers have widely facilitated the exchange of patient and treatment data in almost real time. Today, treatment data can be captured by the cycler and either transmitted the data back to the clinic daily via the Internet or stored on USB drives that patients bring

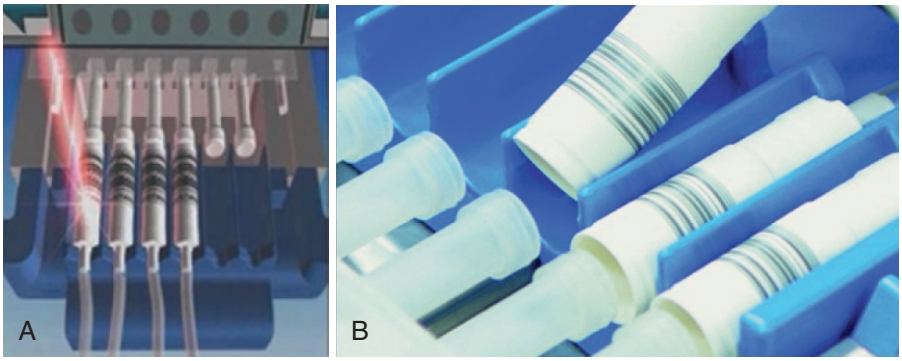
• **Fig. 21.2** Example of a modern gravity-based cycler shown for educational purposes only and not available or approved in all countries. (Courtesy of Fresenius Medical Care North America.)



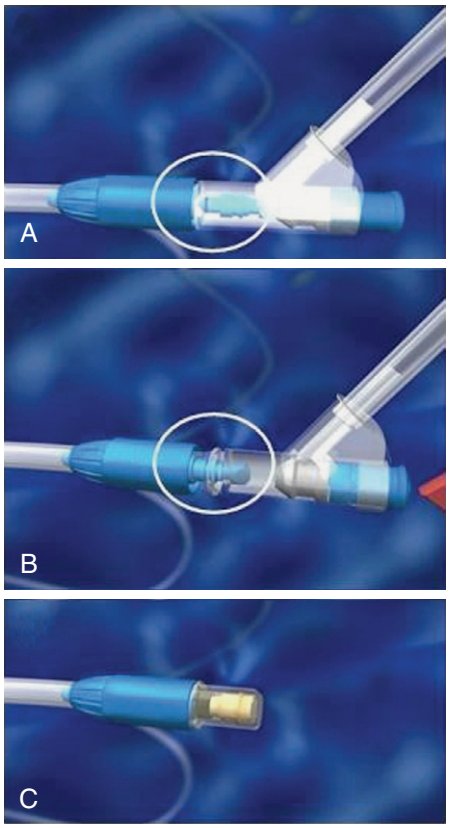
• **Fig. 21.3 Integrated Cassette Systems.** (A) Cassette with heating path, dual fluid chambers, ports for automated bag connectors, and drainage lines. (B) Integration of a peritoneal mechanism with valves and pressure sensors into a disposable fluid management cassette system. (Courtesy of Fresenius Medical Care North America.)



• **Fig. 21.4 Contemporary Pump-Based Cycler Designs.** Examples of contemporary cyclers shown for educational purposes only and are not available or approved in all countries. (Bottom center and right images courtesy of Baxter International Inc. All other images courtesy of Fresenius Medical Care North America.)



• **Fig. 21.5** Connectology. (A) Automated connection device showing an open tray with four bag lines connected to the cycler and bar-code reader. (B) Bag connector with printed bar code. (Courtesy of Fresenius Medical Care North America.)



• **Fig. 21.6** PIN Technology. PIN technology in automated peritoneal dialysis for automatic occlusion of line lumen upon disconnection. (A) Normal position during treatment. (B) The pin is inserted into the catheter extension. (C) Final position with cap. (Courtesy of Fresenius Medical Care North America.)

to the clinic during monthly visits. Some dialysis provider organizations have also developed smartphone apps for patients to use in place of daily flow sheets.

This connected technology gives providers a potentially daily view of therapy adherence and possible treatment issues that can be addressed immediately, instead of waiting for the patient to come to the clinic or call in with concerns. In some connected cyclers, the provider can make immediate changes to the patient's therapy program and push it to the cycler over the Internet. The online portals are customizable, user-friendly interfaces that provide both quick views of multiple patients and detailed views of single treatments.

With the increase in connectivity in medical devices, cybersecurity is of utmost importance. The applicable authorities have issued multiple guidance documents that are intended to reduce the risk of cyberattacks during the exchange of medical data from the device to the clinic. Data encryption with various levels of user rights within the platform ensures that only authorized individuals can access and/or modify information.

In addition to viewing treatment data, online platforms can also be used by technical support teams to troubleshoot and diagnose potential malfunctions of the device.

User Interface and Ease of Use

Much effort has been put into enhancing usability and user experience of modern cyclers. Technology advances include user interfaces with large graphical touchscreen displays, large soft buttons in selectable colors, and soft keypads for entering numerical values. The user-friendly screens allow for easy selection of regimen, times, and volumes. Patients may be guided at all times through on-screen video and audio instructions in the language of their choice. Dialysate fluid bag connections and patient line connections are illustrated in a stepwise manner and explained on the display for easy operation. The incorporation of bar codes has been used to automatically identify the type of solution employed. This information is transmitted to the cycler software, compared with the prescription, and accepted or rejected accordingly. This feature ensures selection of the correct dialysis solution based on the latest prescription. Other approaches to enhance ease of use are integrated voice commands, visual and audio feedback, and alarms.

Cost Considerations

The many models of cyclers on the global market reflect the requirements of different regimens, prescriptions, and availability of funds devoted to kidney replacement therapy in different countries. The convenience and safety offered by the state-of-the-art cycler technology are impressive but not essential to the delivery of adequate care. Compared with manual PD, the use of a cycler necessarily increases the cost of therapy. However, the overall cost of PD is, in general, considerably less than hemodialysis treatments despite the

use of modern cycler technology. Costs can potentially be further minimized or contained by:

1. Using fewer but larger-volume dialysate bags manufactured with less expensive material and simplified packaging
2. Designing simpler tubing sets
3. Reducing the number of necessary connections and other steps that require additional, often expensive, materials to maintain an aseptic environment
4. Reduction of disposables through reutilization of solution bags as drainage bags and the elimination of drain bags by direct disposal of spent dialysate into the sewage lines. Mind that following appropriate safety protocols is essential when considering any reuse of equipment. Depending on the device and manufacturer, reuse may not be recommended and may not be safe with all systems.

Current and Future Developments

Mechanical developments include integration of miniaturized peristaltic mechanisms with valves and pressure sensors into a disposable fluid management cassette system (see Fig. 21.3B), leading to a smaller, more compact cycler design. The disposable cassette may load automatically with silicone membrane valves that can be independently opened and closed using a pin and a small motor to fill or drain the dialysate. The miniaturized cassette plus the high degree of integration of the components can allow a cycler weight below 10 lb with a very small footprint, which may significantly mitigate its intrusiveness in the patient's home and travel limitations.

Some cyclers already offer more flexible prescription options to individualize each single dialysate exchange. One example is adapted PD, where different exchanges within one treatment vary in volume, dwell time, and solution used. This allows an optimized, more patient-specific prescription of these parameters.

New APD systems are in development that will generate PD fluid from concentrates and tap water at the point of care, usually in a patient's home. The potential advantages of such a system include less material handling by patients and greater flexibility between dwell cycles.

Further possibilities emerge through the cloud-based data transfer and connected health platforms. Optimizing patient-specific PD prescriptions through kinetic modeling will be possible without manual data input for systems that are connected to the patients' electronic health records where lab data can be automatically extracted. Since home care means that assistance may be needed at any time, enhanced connectivity and integrated cameras may allow virtual training or patient visits with direct and timely access to the dialysis nurse or the nephrologist.

Conclusions

PD cyclers have evolved into systems that provide much more than automated exchanges for APD. Recent advances allow much-improved integration of information in cloud-based connected health platforms, which greatly facilitates the comprehensive management of PD patients. Modern cyclers have come a long way to become interactive, user-centered medical devices that partner with the patient, nurse, and physician in delivering a highly individualized dialysis treatment and user experience.

Recommended Reading

Diaz-Buxo JA. The road to automated peritoneal dialysis: a personal reflection. *Artif Organs.* 2014;38(12):993–997.

Provides an overview of the evolution and development of APD.

Chaudhry R, Golper T. Automated cyclers used in peritoneal dialysis: technical aspects for the clinician. *Med Devices.* 2015;8:95–102.

A review of the technical and clinical aspects of PD cyclers.

K/DOQI. US Commentary on the 2020 ISPD practice recommendations for prescribing high-quality goal-directed peritoneal dialysis. *Am J Kidney Dis.* 2021;77(2):157–171.

Summarizes the current recommendations for adequate peritoneal dialysis.

22

Peritoneal Dialysis Solutions

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Introduction

Peritoneal dialysis (PD) is a form of home-based kidney replacement therapy (KRT) used to treat patients suffering from kidney failure. Small solute and fluid removal are achieved using diffusion and convection across the peritoneal membrane, enabled by PD solutions.[1] Understanding the principles behind PD solution compositions and their mechanisms of action is central to ensuring safe and effective prescribing of PD to optimize patient outcomes. In this chapter, we will describe the three essential components of PD solutions (electrolytes, buffers, and osmotic agents), the four main types of PD solutions currently in use (conventional PD solutions, icodextrin, amino acid PD solutions, and neutral-pH, low–glucose degradation product [GDP] solutions), and promising PD solutions in development.

Electrolytes

Sodium

Sodium overload complicated by fluid overload and hypertension commonly occurs in patients with kidney failure, including those receiving PD, particularly those with fast peritoneal solute transfer rates or low levels of residual kidney function.[2] Removal of sodium in PD is achieved primarily by convection through ultrafiltration.[3] Generally, the sodium concentration in PD solutions is 131–134 mmol/L.[4] With a standard sodium PD solution prescribed for 8L/day, approximately 1.68 g (73.08 mmol) of sodium can be expected to be removed from the body.[3] Other factors reported to promote sodium removal include achieving higher ultrafiltration volume (e.g., by higher prescribed exchange volumes, higher PD solution glucose concentrations) and shorter dwell time (particularly in fast peritoneal solute transfer rates).[5]

An alternative strategy for augmenting peritoneal sodium removal is the use of low-sodium PD solutions (125 mmol/L). In a multicenter randomized controlled trial of low-sodium PD solution (125 mmol/L) versus standard-sodium PD solution (134 mmol/L) in 82 hypertensive PD patients from 17 sites, the low-sodium PD regimen resulted in higher mean daily sodium removal (0.39 g) compared to the standard-sodium solution at 12 weeks and a decrease in both systolic and diastolic blood pressure by 11 and 5 mm Hg, respectively, thereby allowing reduction in antihypertensive medication usage.[3] The standard-sodium solution resulted in lower daily sodium removal (0.07 g), minor decrease of systolic blood pressure (1 mmHg), and no change in diastolic blood pressure at 12 weeks.[3] These promising results are, however, based on relatively small size trials, such that the applicability and effectiveness of low-sodium PD solutions in broader clinical settings have not yet been demonstrated.

Potassium

Patients with CKD often suffer from hyperkalemia due to a decrease in kidney clearance. PD solutions typically do not contain any potassium in order to maximize the concentration gradient across the peritoneal membrane, thereby promoting potassium diffusion into the peritoneal fluid. On average, daily peritoneal potassium removal in PD patients is estimated to be of the order of 30.4 mmol/day and is directly proportional to the dwell time of each exchange.[6] Potassium removal is also dependent on residual kidney function, intracellular volume, and dietary intake in patients receiving PD.[6] Intracellular volume and dietary intake were shown to have a positive correlation with serum potassium level, while residual kidney function and dialysis exchanges had a negative correlation with serum potassium level.[6]

Calcium

There are three levels of calcium available in commercially manufactured dextrose-based PD solutions: 1 mmol/L, 1.25 mmol/L, and 1.75 mmol/L (Table 22.1). Most commonly, PD solutions with 1.25 mmol/L calcium are

TABLE 22.1 Types of Peritoneal Dialysis Solutions

Characteristic	Composition
Osmotic agent	Dextrose (1.5%, 2.5%, 4.25%)
	Icodextrin (7.5%)
	Amino acid (1.1%)
Volume of PD solution	Dextrose: 1 L*; 1.5 L; 2 L; 2.5 L; and 3 L
	Icodextrin: 2 L; 2.5 L
	Amino acid: 2 L; 2.5 L
	Neutral pH, low glucose degradation product (Physioneal): 5 L (3.75 L glucose chamber and 1.25 L buffer chamber)
	Cycler bags are available in 3 L, 5 L, and 6 L.
Ionized calcium level	1 mmol/L; 1.25 mmol/L; 1.75 mmol/L
	(2 mEq/L; 2.5 mEq/L; 3.5 mEq/L)
Buffer	Lactate (40 mEq/L)
	Bicarbonate/lactate (25/15 mEq/L in most countries, 25/10 mEq/L in Japan)
	Bicarbonate (34 mEq/L)
Bag configuration	Single or dual chamber

PD, Peritoneal dialysis.
* 1-L size is not available in the United States.

used for treatment unless there are clinical indications to use high-calcium (1.75 mmol/L) PD solutions (e.g., hypocalcemia, such as may occur following parathyroidectomy) or low-calcium (1.00 mmol/L) solutions (e.g., hypercalcemia). A glucose polymer PD solution, icodextrin, is currently only available with a 1.75 mmol/L calcium concentration.

Magnesium

Hypermagnesemia can be seen among patients with kidney failure because magnesium is normally excreted by the kidney. Most commonly, PD solutions contain 0.25 mmol/L of magnesium to increase their clearance. The removal of magnesium can be further promoted by the use of higher glucose concentration PD solution to achieve greater ultrafiltration volume.[7] However, the extent of removal needs to be carefully considered as hypomagnesemia (< 1.8 mg/dL) has been shown to be a risk factor for hospitalization.[8]

Buffers

Buffers are an essential component of PD solutions that serve to correct acidosis arising from reduced kidney excretion of hydrogen ions generated by the body's metabolic processes.[9,4] They are available in three forms: nonbicarbonate buffers, bicarbonate-lactate buffers, and bicarbonate-only buffers. Among the nonbicarbonate buffers (i.e., lactate, acetate, and pyruvate), lactate has been used widely because of its stability and favorable safety profile. Once absorbed, it is metabolized into bicarbonate via the glycolytic pathway.[10] Although tolerated well, lactate has been associated with several adverse outcomes, including muscle breakdown, reduced myocardial contractility, reduced peritoneal host defenses, and impaired viability of peritoneal cells.[11]

Bicarbonate is a more physiological buffer but was initially superseded by lactate due to problems with the precipitation of calcium carbonate from alkalinization during heat sterilization. The development of double chamber systems has allowed separation of bicarbonate and calcium, thereby avoiding the risk of precipitation. Therefore, currently available PD solutions offer various options of buffer, including lactate, lactate/bicarbonate, and pure bicarbonate buffers. Some investigators have reported better preservation of peritoneal membrane function among patients receiving pure bicarbonate buffer PD solutions compared to those containing lactate, as evidenced by increased ultrafiltration capacity over a 10-month period (4.89 mL/g glucose at baseline and 5.13 mL/g glucose at month 10).[12] However, the effect of any particular buffer on peritoneal membrane preservation has been inconclusive due to the small number of short-term trials.[13]

Osmotic Agents

Glucose has been widely used as the osmotic agent in PD solutions because it is metabolized easily, readily available, inexpensive, and can be sterilized.[14] Ultrafiltration is achieved by the osmotic gradient generated by glucose, allowing the movement of the fluid through the pores of the peritoneal membrane.[15] However, the use of glucose in PD solutions is associated with systemic glucose absorption, which may result in hyperglycemia and dyslipidemia.[14]

Therefore, other agents such as xylitol and fructose have been proposed as alternative osmotic agents in PD solutions. However, the risks of harm from hyperosmolar status with altered consciousness and increases in the levels of lactic and uric acids have prohibited their use.[16] There are ongoing efforts to identify a safe, effective, and cost-efficient osmotic agent to replace glucose, including taurine[17] and hyperbranched polyglycerol.[18] However, most of these studies are currently largely restricted to the preclinical area, and glucose continues to be the preferred osmotic agent at present.

Icodextrin is a starch-derived, branched, water-soluble glucose polymer, which has been introduced as a glucose-sparing alternative osmotic agent. It is used to facilitate fluid removal during long PD dwells (particularly in people with fast peritoneal solute transfer rate), reduce glucose load, particularly in patients with diabetes, and perhaps preserve peritoneal membrane function.[19]

Besides being used as a short-term treatment for PD patients with protein-energy wasting, amino acid is also used as an osmotic agent in PD solutions. It was first introduced in 1968 by Gjessing as an addition to intravenous fluid used for PD. Later, Oreopoulos and the team used amino acid to substitute glucose in PD solution as the osmotic agent. They discovered that amino acid had reasonable ultrafiltration capacity and was as efficient as glucose in removing urea, creatinine, and potassium without impairing peritoneal membrane function. An amino acid-based solution was also suggested to have a beneficial nutritional effect in patients who had low protein intake and hypalbuminemia. However, it was also revealed to have side effects, such as increased peritoneal permeability and protein loss, increased acidemia, increased azotemia, nausea and vomiting, loss of appetite, and also amino acid toxicity. Therefore, it is proposed that amino acids should be used no more than once daily together with other osmotic substances, such as glucose and icodextrin.[20] Amino acid-based solutions have not been approved by the Food and Drug Administration and are not commercially available in the United States.

Peritoneal Dialysis Solutions

All PD solutions contain an osmotic agent, buffer, and electrolytes, as described previously. They can be broadly classified into four groups according to their compositional characteristics: conventional PD solutions, icodextrin, amino acid solutions, and neutral-pH, low-GDP (biocompatible) PD solutions (Table 22.2).

Conventional Peritoneal Dialysis Solutions

Conventional PD solutions are the most commonly used type of PD solutions and employ glucose as their main osmotic agent. These solutions are recognized for their unphysiologic characteristics, including acidic pH, high osmolality, high lactate concentrations, and high glucose concentrations.[21] These undesirable properties have been shown in studies to result in several unfavorable outcomes, including mesothelial cell death, peritoneal injury, and nephrotoxicity,[22,21] which have been attributed to exposure to the high levels of GDPs found in these solutions. GDPs are generated during heat sterilization of PD solutions and during prolonged storage, particularly in the setting of higher storage temperatures and polyvinyl chloride containers (as opposed to Clear-Flex or Biofine containers).[16] GDPs may increase threefold during an 18-month storage period.[23] Peritoneal membrane exposure to GDPs leads to deposition of peritoneal advanced glycation end products (AGEs), which in turn trigger oxidative stress and inflammation.[19] Systemic absorption of GDPs may also lead to kidney injury.[24]

The concentrations of monohydrous glucose commonly employed in PD solutions are 1.5% (354 mOsm/L), 2.5% (395 mOsm/L), and 4.25% (484 mOsm/L).[25] When specified as anhydrous glucose, the corresponding concentrations are 1.36%, 2.27%, and 3.86%. A higher glucose content (or tonicity) will result in greater ultrafiltration, and PD solutions containing 1.5% dextrose, 2.5% dextrose, and 4.25% dextrose can remove approximately 100–200 mL, 200–500 mL, and 500–1000 mL of ultrafiltration, respectively. However, the high glucose content in the solution may lead to several unwanted effects (Box 22.1). Approximately 120–212 g of glucose (equivalent to 500 to 800 kcal) can be absorbed from exposure to these conventional PD solutions daily. The extent of systemic glucose absorption increases with increasing glucose concentration, faster peritoneal solute transfer rate, and longer dwell duration.[26] This glucose absorption could, in turn, lead to metabolic complications, such as dyslipidemia, and vascular complications, such as coronary artery disease.[19] Therefore, the International Society for Peritoneal Dialysis (ISPD) guidelines recommend the use of glucose-sparing strategies (such as substituting icodextrin and/or amino acid for glucose) and biocompatible (neutral pH, low GDP) solutions to mitigate the systemic complications of conventional PD solutions.[27,28]

Icodextrin Solution

Icodextrin (Extraneal) induces sustained ultrafiltration over prolonged periods by colloid osmosis. It is absorbed more slowly than glucose and most absorption from the peritoneal cavity occurs via the lymphatic system. Thereafter, it is hydrolyzed to maltose, maltotriose, maltotetraose, and other metabolites, which persist in the blood circulation for some time.[29,19] Consequently, icodextrin is ideally prescribed once per day for a long dwell period (e.g., overnight for 8–10 hours).

Although icodextrin is typically administered once daily to avoid excessive serum maltose accumulation, some studies have examined the value of twice-daily icodextrin exchanges.[30] A small study in 2011 investigated the efficacy of administering two exchanges of icodextrin per day in patients with ultrafiltration failure after long-term PD, which resulted in reductions of both volume overload and glucose exposure in their subjects.[29] However, using icodextrin more than once per day is still not recommended due to the lack of long-term safety data, particularly in relation to the effects of maltose exposure.

Icodextrin is indicated for patients who have ultrafiltration failure or those who need optimization of their fluid status, particularly patients with high or high-average peritoneal solute transfer rates.[13] A recently published Cochrane systematic review and meta-analysis of randomized controlled trials demonstrated that icodextrin led to a 70% reduction in episodes of uncontrolled fluid overload and an approximate 450mL increase in daily ultrafiltration compared with glucose-based solutions; although, its effects on other patient-important outcomes (such as technique failure) were uncertain.[13] ISPD guidelines recommend using icodextrin once a day as an alternative to glucose solutions for long dwell in PD patients with inadequate peritoneal ultrafiltration.[27]

TABLE 22.2 Characteristics of Peritoneal Dialysis Solutions

PD solution	Base	Benefits	Drawbacks/Adverse Effects	Indication	Cost	Availability
Conventional PD (Dianeal, Andy-disk or Stay-safe)	Dextrose	Low cost	• Poor biocompatibility • Infusion pain due to low pH	• Routine peritoneal dialysis	GBP 3.9/ USD 6	Widely available
Icodextrin (Extraneal)	Polymaltose glucose polymers	• Higher ultrafiltration • Lower risk of hyperglycemia • Better metabolic profile • Excellent clearance of solutes • Positive sodium removal • No GDP exposure	• Recommended for use once daily • Infusion pain due to low pH • Underestimation of blood glucose level when using glucometers based on glucose dehydrogenase pyrroloquinoline quinone method (e.g., Advantage, Accucheck, Glucotrend) • Underestimation of serum amylase level (i.e., falsely low readings) • Hypersensitivity (skin rash, sterile peritonitis) • Mild hyponatremia	• Ultrafiltration failure with dextrose-based solutions • Patients who need optimal fluid status, particularly patients with high or high-average peritoneal membrane solute transfer rates • Improved glycemic control in PD patients with diabetes • Heart failure patients (who are resistant to diuretics)	GBP 6.6/ USD 10	Widely available
Amino acid (Nutrineal)	Amino acid	• Can be used as nutritional support • No GDP exposure	• Can be used only once daily • Infusion pain • Dose-dependent nausea • Vomiting • Uremic symptoms • Mild metabolic acidosis	• PD patients with protein-energy wasting (short-term use) • As part of a glucose-sparing PD-regimen	GBP 8.5/ USD 13	Limited
Neutral pH. Low GDP (Physioneal/ Reguneal, Bicavera)	Bicarbonate/ lactate buffer	• More biocompatible • Preserved residual kidney function • Improvement of urine volume • Prevention of peritonitis • Prevention of infusion pain	• Underestimation of blood glucose level and serum amylase level • Mild hyponatremia	• PD patients who have inflow pain • Preservation of residual kidney function	GBP 7.3/ USD 11	Limited

GDP, Glucose degradation product; *PD*, peritoneal dialysis.

Several rare side effects of icodextrin have been reported, such as allergic reactions manifesting as skin rash and sterile peritonitis due to contamination with peptidoglycan.[31] Additionally, icodextrin is metabolized into maltose and maltotriose, which accumulates and may result in false-positive hyperglycemia on glucometers that use the glucose dehydrogenase pyrroloquinoline quinone (GDH PQQ) method. This false-positive hyperglycemia may lead to excessive administration of insulin or other hypoglycemic agents and ultimately cause hypoglycemia.[14]

Amino Acid Solution

Amino acid PD solutions were primarily introduced for the short-term treatment of protein-energy wasting but more recently have also been used in glucose-sparing PD regimens.[19] The most common commercially available form

• BOX 22.1 Advantages and Disadvantages of Conventional Peritoneal Dialysis Solutions

Advantages

- Long-term safety
- Nutritional supplement in patients with protein-energy wasting

Disadvantages

- Reduced peritoneal defenses
- Glucose-induced peritoneal fibrosis
- Non-physiological pH and hyperosmolality
- Generation of GDPs
- Higher risk of residual kidney function decline
- Possible adverse systemic effects on glucose and lipid metabolism

GDP, Glucose degradation product.

is Nutrineal, which contains 87 mmol/L amino acids (61% essential).[4] With an osmolality of 365 mOsm/L, the solution provides equivalent ultrafiltration to a 1.5% glucose PD solution.[19] It is administered once daily concurrent with the largest meal of the day (e.g., lunch or dinner). This leads to the absorption of approximately 18 g of amino acid (or 25% of a PD patient's required protein intake of 1.2 g/kg/day) and may be useful in the PD setting since approximately 20%–70% PD patients have protein-energy wasting and have high daily protein losses into their PD effluent (4–8 g/day).[19] Consequently, only one exchange per day of amino acid solution has been considered a reasonable nutritional intervention in appropriate patients, with monitoring of adequate caloric intake.[32] The largest randomized controlled trial to date involved 60 continuous ambulatory PD (CAPD) patients with protein-energy wasting followed over a 3-year period and did not observe any benefit of amino acid dialysates over standard fluids with respect to composite nutritional indices, daily ultrafiltration volumes, small solute clearances, technique survival, or patient survival. It should also be noted that amino acid PD solutions can lead to acidosis and elevated serum urea concentrations, such that patients on these solutions should be monitored closely.[33]

More recently, substituting an amino acid PD solution for a glucose exchange each day has been used as a strategy for reducing glucose exposure and improving metabolic parameters, particularly in PD patients with diabetes mellitus. A short-term (8-week) study of amino acid versus glucose PD solution in 22 PD patients led to significant reductions in serum cholesterol and triglyceride concentrations.[34] In the IMPENDIA/EDEN trial (IMPENDIA trial: combination of dextrose-based solution, icodextrin, and amino acids; EDEN trial: a different dextrose-based solution, icodextrin, and amino acids), amino acid PD solution in combination with icodextrin and a dextrose-based solution resulted in a significant 0.5% reduction in the primary end-point of glycated hemoglobin compared with glucose-only PD solutions.[35] However, counterbalanced against this finding, deaths and adverse events related to fluid volume expansion were increased in the glucose-sparing intervention group. Moreover, the effects of amino acid solution on long-term peritoneal membrane preservation are still uncertain.[36] Therefore, incorporating amino acid PD solutions into glucose-sparing PD regimens cannot be routinely recommended at this stage. Amino acid solutions have not been approved by the U.S. Food and Drug Administration and are not commercially available in the United States.

Neutral-pH, Low-Glucose Degradation Product (Biocompatible) Peritoneal Dialysis Solutions

Neutral-pH, low-GDP solutions are PD solutions with multichamber bag systems in which the compartment containing glucose has a very low pH (pH 2.8–3.1), which prevents the formation of GDPs during heat sterilization and storage. The seal(s) separating each chamber are broken to facilitate mixture of glucose-containing solution with bicarbonate-containing solution to form a final neutral-pH (7.0–7.4), low-GDP PD solution immediately prior to use (Table 22.3).[32] The neutral-pH, low-GDP solutions that are currently available can be categorized into those with low GDP content (Physioneal/Reguneal from Baxter Healthcare, United States) and those with ultralow (< 80 μmol/L) GDP content (Balance or Bicavera by Fresenius Medical Care, Germany).[19] Neither of these two solutions are commercially available in the United States. Preclinical studies have reported an improvement in cellular function and better preservation of peritoneal membrane from exposure to these solutions. To date, there have been 29 randomized controlled trials that have evaluated the effect of treating patients on PD with biocompatible PD solutions. A recent systematic review and meta-analysis of these trials[13] have demonstrated that use of a neutral-pH, low-GDP PD solution improves residual kidney function in patients receiving PD regardless of their follow-up duration (standardized mean difference [MD], 0.19; 95% confidence interval [CI], 0.05 to 0.33; approximated to an MD in glomerular filtration rate (GFR) of 0.54 mL/min/1.73 m^2 [95% CI 0.14–0.93]). Due to the large number of studies using one type of neutral-pH, low-GDP PD solution, a subgroup analysis according to the different types of PD solutions was unable to determine whether there is a difference in residual kidney function. Similar benefits were observed for daily residual diuresis (11 studies, 791 participants; MD, 114.37mL/day; 95% CI, 47.09 to 181.65). However, the benefit became more pronounced with a longer follow-up duration greater than 1 year. It has been argued that some of the residual kidney function benefit from using neutral-pH, low-GDP solutions may be due to reduced peritoneal ultrafiltration (9 studies, 414 participants; estimated MD, –69.72mL/4 hours; 95% CI, –122.84 to –16.60). However, there was moderate heterogeneity (I^2 = 51%) associated with this finding, suggesting that the evidence is of low certainty. Neutral-pH, low-GDP solutions may also reduce inflow pain (low certainty evidence).[13] However, the effects of neutral-pH, low-GDP solutions on other patient-important outcomes, such as peritonitis, peritoneal solute transport rate, technique survival, and patient survival, remain uncertain.[13]

TABLE 22.3 Composition of Peritoneal Dialysis Solutions

Manufacturer		Baxter				Fresenius Medical Care		
Product Name		Dianeal	Physioneal/ Reguneal	Extraneal	Nutrineal	Delflex	Bicavera	Balance
Chamber		Single	Double	Single	Single	Single	Double	Double
Composition	Glucose					+	+	+
	Dextrose	+	+					
	Icodextrin			+				
	Amino acid				+			
	Sodium	+	+	+	+	+	+	+
	Calcium	+	+	+	+	+	+	+
	Magnesium	+	+	+	+	+	+	+
	Chloride	+	+	+	+	+	+	+
	Lactate	+		+	+	+		+
	Bicarbonate/ lactate		+					
	Pure bicarbonate						+	
pH		5.2–5.5	7.4	5.5	6.7	7.0	7.4	7.0
Osmolality (mOsm/kg)		358–511	358–511	284	365	344–486	358–511	358–511
GDP (3-desoxyglycosone)		525 μmol/L	253 μmol/L	N/A	N/A	N/A	42 μmol/L	42 μmol/L
Glucose-sparing PD solution				+	+			

+ indicates yes.
GDP, Glucose degradation product; *N/A*, not applicable; *PD*, peritoneal dialysis.

Future Peritoneal Dialysis Solutions

A mixture of 1.4% glycerol, 0.5% amino acids, and 1.1% dextrose was associated with improved preservation of peritoneal membrane in a rat model of CKD.[37] Glycerol is a low-molecular-weight substance of sugar alcohol, which produces initial higher ultrafiltration compared to glucose. However, due to its low molecular weight causing rapid absorption, the final result of ultrafiltration is lower than the initial.[4] Another proposed substance is L-carnitine as an osmotic agent, which is suggested to enhance ultrafiltration.[38] Hyperbranched polyglycerol has been investigated as the new osmotic agent in PD solution. The latest study comparing hyperbranched polyglycerol with Physioneal in rats showed that within 3 months of exposure, hyperbranched polyglycerol did not alter peritoneal membrane function as well as induced less inflammatory and tissue growth factor, thus preserving peritoneal membrane function and structure. Currently, its metabolic and pharmacokinetic pathways are being studied to assure the long-term safety in patients with compromised kidney function.[18]

Conclusions

There are three essential components of PD solutions: electrolytes, buffers, and osmotic agents. Conventional PD solution has been the most commonly used solution; however, it is associated with adverse effects including atherogenic and diabetogenic effects, dyslipidemia, impaired peritoneal defenses, glucose-induced peritoneal fibrosis, declining residual kidney function, nonphysiological pH, hyperosmolality, and generation of GDPs. Other various solutions have been investigated and utilized to address this problem. Icodextrin is effective in augmenting ultrafiltration, reducing fluid overload, and possibly improving glycemic control in patients with diabetes. Amino acid solutions have not been shown to be effective as a nutritional intervention and cannot be routinely recommended for this purpose or as a glucose-sparing strategy presently. Neutral-pH, low-GDP solutions lead to better preservation of residual kidney function, but their long-term effects on other patient-important outcomes remain uncertain. Therefore, there is an important need to develop more "biocompatible" PD solutions, and experimental works are currently ongoing.

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23

Solute Management With Peritoneal Dialysis

JENNY I. SHEN, MD, MS

Introduction

One of the primary purposes of peritoneal dialysis (PD) is to clear solutes that are normally removed by the kidney. In this chapter, we will discuss the determinants of solute clearance, how to measure and evaluate it, and how to adjust the prescription to increase solute clearance.

Determinants of Solute Clearance

Solutes are cleared from the body when they move from the capillaries in the peritoneal membrane into the dialysate dwelling in the peritoneal cavity. This happens primarily through diffusion but also through convection with ultrafiltration.

Several factors affect clearance. One is the difference in the **concentration** of the solute between the dialysate and the blood: the greater the concentration gradient, the faster the clearance. Another is **surface area**, with more surface area leading to higher rates of clearance. Because adhesions decrease the surface area of the peritoneal membrane, individuals with a history of extensive abdominal surgeries may have lower rates of clearance. Conversely, increased vascularity or density of capillaries in the membrane will increase clearance.

Clearance is also affected by the **size** of the solute. One of the principles of diffusion is that the larger the solute, the more slowly it will diffuse. Solute transfer across the peritoneum is even more dependent on size due to the different types of pores through which molecules move. This system of pores is described by the Three Pore Model. The smallest type of pore is the ultrasmall pore or aquaporin-1 channel. These pores are only 4–6 angstroms wide and only allow passage of water molecules. Solutes that are 40–-60 angstroms, such as urea, move through a second type of pore, small pores. These are the most common type of pore and make up 95% of the pore surface area of the peritoneum. By contrast, there are relatively few large pores, the third type of pore, which allows for the movement of solutes 100–200 angstroms in size, such as proteins. Large pores make up only 2% of the pore surface area. For this reason, it takes longer for larger solutes to be cleared. This is demonstrated in Fig. 23.1. At any given point in time, the clearance of urea, which is 60 daltons, is higher than creatinine, which is 113 daltons. Both are cleared much more readily than middle molecules, which are only significantly cleared with long dwells of at least 8 hours.

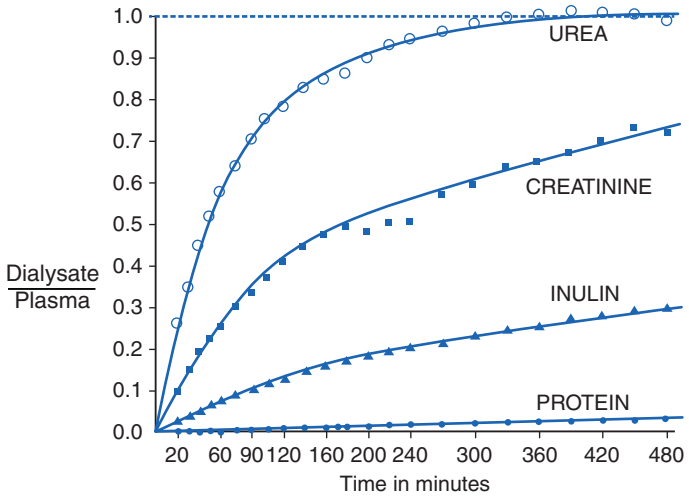
Two other major determinants of clearance, volume of dialysate and time, can be explained by the equation to calculate clearance:

$$DV / P$$

where D = the concentration of the solute in the dialysate after a certain amount of time, V = the volume of dialysate drained after this time period, and P = the concentration of the solute in the plasma. For the same D/P, the higher the **volume** of dialysate, the higher the clearance. For these reasons, larger dwell volumes provide more clearance for small solutes. However, because of their larger size, the clearance of middle molecules is not significantly increased with larger fill volumes.

D/P varies by **time**. When the PD solution is first instilled, D/P = 0 for solutes that are not present in the PD solution, such as urea and creatinine. Over time, D/P approaches 1 as the solute diffuses into the dialysate, and the solute concentration equilibrates between the plasma and dialysate.

The rate at which D/P changes over time varies by individual and depends on the peritoneal membrane transport status. This can be measured with the peritoneal equilibration test (PET). The PET measures the dialysate concentration of creatinine and glucose at the beginning, middle, and end of a standardized 4-hour exchange and the plasma concentration of creatinine at the middle of the exchange (Box 23.1). First, an 8–12-hour overnight dwell is drained over at least 20 minutes. Then, 2 L of a 2.5% dextrose solution is instilled over 10 minutes. Once all of the fluid has been infused, 200 mL is immediately drained, mixed by inverting the container a few times, and 10 mL is removed to measure solute concentrations at time 0. The remain-



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• **Fig. 23.1** Dialysate/plasma concentration ratios (D/P) for urea, creatinine, inulin, and protein from samples through an 8-hour dwell. Urea, the smallest molecule at just 60 daltons, diffuses into the dialysate the fastest, and thus, the D/P approaches 1 in the shortest amount of time, reaching above 0.9 by 240 minutes. Creatinine, at 113 daltons, is only about 70% equilibrated at 240 minutes. Both are cleared much more readily than middle molecules like inulin and proteins which have D/P < 0.30 even after 480 minutes. (Data from Popovich RP, Moncrief JW, Nolph KD, et al. Continuous ambulatory peritoneal dialysis. *Ann Intern Med*. 1978; 88(4):449–456.)

• BOX 23.1 Peritoneal Equilibration Test Procedure

1. Drain 8–12-hour-long dwell over 20 minutes.
2. Instill 2 L 2.5% dextrose solution over 10 minutes.
3. Collect dialysate sample for time 0.
   a. Immediately drain 200 mL.
   b. Mix by inverting sample several times.
   c. Collect 10 mL.
   d. Reinstill the remaining 190 mL.
4. After 2 hours of ambulation, collect dialysate sample for 2-hour sample using the same procedure as earlier.
5. Draw blood sample at the same time.
6. After a total of 4 hours of dwell time, completely drain the dialysate while the patient is upright over 20 minutes.
7. Weigh the collection.
8. Collect a 10-mL sample of dialysate for the 4-hour sample.

ing 190 mL is reinstilled. The individual is encouraged to move around for the next 2 hours, after which time another 200 mL is drained and mixed, 10 mL is collected for measurements, and the remainder of the fluid is reinfused. A blood sample is drawn at this time to measure plasma solute concentrations. After another 2 hours (for a total 4-hour dwell time), the dialysate is completely drained over 20 minutes while the individual is upright. The volume of the collection is measured, and 10 mL is sampled for measurement of the 4-hour dialysate concentrations.

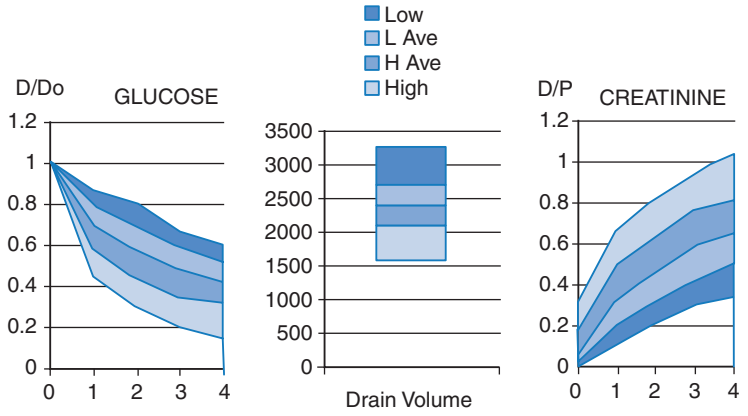
The dialysate and blood samples are measured to calculate the equilibration ratios of creatinine and glucose. Equilibration ratios of creatinine are equal to the ratio of the dialysate to serum concentration of creatinine (D/P) at times 0, 2, and 4 hours. Since glucose is quickly metabolized after it is absorbed from the dialysate into the blood, measuring serum samples of glucose will not reflect the rate of transfer of glucose across the peritoneum. Instead, the equilibration ratios of glucose are calculated as the ratio of the dialysate concentration of glucose at times 2 and 4 hours to the glucose concentration in the dialysate at times 0 (D/D_0).

Individuals are characterized depending on how their equilibration ratios compare to a reference distribution of values (Fig. 23.2). The faster creatinine is cleared, the higher the dialysate concentration of creatinine, and thus, the D/P creatinine will be at a given time. For this reason, individuals whose creatinine D/P are > 1 standard deviation above the mean are classified as individuals with **fast or high peritoneal solute transfer rates**, and those that are < 1 standard deviation below the mean are classified as people with **slow or low peritoneal solute transfer rate**. Those with creatinine D/P within a standard deviation above or below the mean are considered to have average peritoneal solute transfer rates, respectively.

The faster glucose is transferred from the dialysate to the blood, the lower the D/D_0 will be at a given time. So, when classifying peritoneal membrane based on equilibration ratios for glucose, people with faster peritoneal solute transfer rates have D/D_0 glucose > 1 standard deviation *below* the mean, those with slower peritoneal solute transfer rates have a ratio < 1 standard deviation *above* the mean, and those with average peritoneal solute transfer rates have ratios within a standard deviation below or above the mean, respectively.

Creatinine D/P and glucose D/D_0 should be correlated. A serum glucose concentration > 235 mg/dL will result in inaccurate glucose equilibration ratios; in this case, only the creatinine D/P should be used. If the ratios lead to discordant categorization of peritoneal membrane, the test should be repeated.

People with a faster peritoneal solute transfer rate will quickly clear their solutes, with maximal clearance of



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• **Fig. 23.2** Characterization of the Peritoneal Membrane Function With Results of the Peritoneal Equilibration Test (PET). Equilibration ratios for creatinine (dialysate to plasma concentration of creatinine, or D/P) and glucose (dialysate concentration at time *t* to the dialysate concentration at time 0, or D/D_0) are plotted at 2 and 4 hours of a 4-hour dwell. The faster creatinine is cleared, the higher the dialysate concentration of creatinine, and thus the D/P creatinine, will be at a given time. For this reason, individuals whose creatinine D/P are >1 standard deviation above the mean are classified as having fast peritoneal solute transfer rate (PSTR), and those that are <1 standard deviation below the mean are classified as with slow PSTR. Those with creatinine D/P within a standard deviation above or below the mean are considered to have average PSTR. The faster glucose is absorbed from the dialysate to the blood, the lower the D/D_0 will be at a given time. So, when classifying PSTR based on equilibration ratios for glucose, PSTR is fast if D/D0 glucose >1 standard deviation below the mean, PSTR is slow if the ratio <1 standard deviation above the mean, and those with average PSTR have ratios within a standard deviation below or above the mean, respectively. (Data from Twardowski ZJ, Nolph KO, Khanna R, et al. Peritoneal equilibration test. *Perit Dial Int*. 1987;7(3):138–148.)

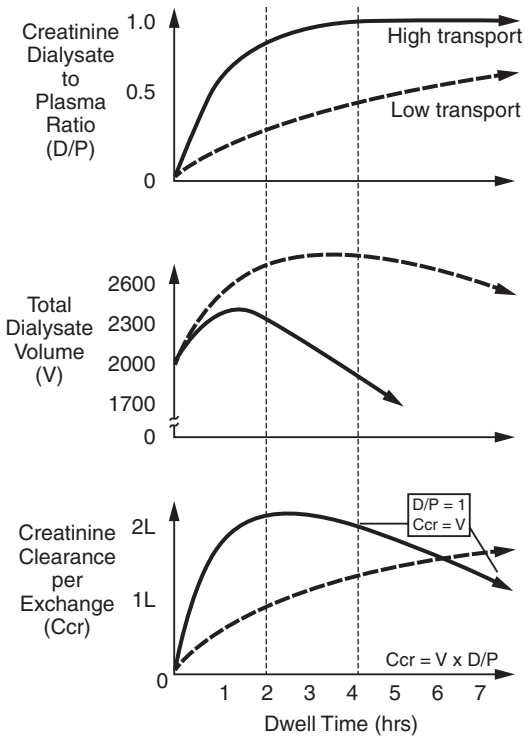
small molecules around three to four hours (Table 23.1, Fig. 23.3). They will also equilibrate glucose more quickly. Since ultrafiltration depends on the difference in the concentration of glucose between the dialysate and serum, this means that people with faster peritoneal solute transfer rates will maximally ultrafiltrate relatively quickly, after which time they may start to reabsorb fluid. Since clearance depends on the volume of dialysate removed, reabsorption reduces solute clearance. Convective clearance is also lower when ultrafiltration is limited. For this reason, faster peritoneal solute transfer rate will achieve maximal clearance with shorter dwells. People with slower peritoneal solute transfer rate, on the other hand, need more time to clear their solutes and continue to ultrafilter throughout longer dwells, resulting in better clearance with longer dwells.

Membrane function can change over time. Because changes are known to commonly occur from the first to fourth week of starting PD, a baseline PET is best performed after the individual has been on dialysis for at least 2 to 4 weeks. Episodes of peritonitis can acutely increase peritoneal solute

TABLE 23.1 Response to Standard-Dose Continuous Ambulatory Peritoneal Dialysis (CAPD) by Transport Status

Peritoneal Solute Transfer Rate (PSTR)	Ultrafiltration	Clearance	Recommended Prescription
High/fast	Poor	Adequate	Short dwells (<3 hours)
			Consider cycler
			Consider icodextrin for longer dwells
Average	High	Adequate to inadequate	Average dwells (2–5 hours)
			May need continuous PD (no dry period)
Low/slow	Excellent	Inadequate in anuric large individuals	Long (>4 hours), higher volume dwells
			Likely need continuous PD (no dry period)

PD, Peritoneal dialysis.
Adapted from Twardowski ZJ. PET—a simpler approach for determining prescriptions for adequate dialysis therapy. *Adv Perit Dial*. 1990;6:186-191.



• **Fig. 23.3** Differences in Clearance and Ultrafiltration Between People With Fast and Slow Peritoneal Solute Transfer Rates (PSTRs). People with fast PSTRs clear their solute faster, reaching equilibration ratios of 1 sooner than those with slow PSTRs. They also equilibrate their glucose more quickly with maximal ultrafiltration around 2 hours, after which time they will start to reabsorb the dialysate. The combination of these two processes means that the creatinine clearance with a fast PSTR will start to fall after about 4 hours of dwell time, making shorter exchanges most ideal. People with slow PSTRs, on the other hand, will continue to clear creatinine past 4 hours, making longer dwell times better for improving clearance. (Data from Twardowsky ZJ. Nightly peritoneal dialysis: why, who, how, and when? *ASAIO Trans*. 1990;36:8.)

transfer rates. Over the long-term, even in the absence of peritonitis, peritoneal solute transfer rates can increase in what has been called type I membrane failure, resulting in reduced ultrafiltration. This is likely due to angiogenesis, which increases the surface area available for transport. The opposite, type II membrane failure can also occur in which peritoneal solute transfer rate decreases, resulting in a drop in both fluid and solute removal. This may be a result of repeated or severe episodes of peritonitis that result in adhesions and, thus, a decrease in the peritoneal membrane surface area for solute transfer. In rare cases, it is associated with encapsulating peritoneal sclerosis, a sometimes fatal condition in which the adhesions lead to intestinal obstruction.

Measuring Solute Clearance

Solute clearance can be assessed both subjectively and objectively. When uremic toxins are insufficiently cleared, individuals can exhibit subjective symptoms of uremia. These include fatigue, nausea, vomiting, decreased appetite, difficulty sleeping, pruritus, difficulty concentrating, depression or irritability, and pain.

Because of the nonspecific nature of uremic symptoms, it is often easier to assess whether they are attributable to decreased solute clearance by correlating them with changes in objective measures like serum concentrations of solutes known to be cleared by PD. The most common measure of the clearance of uremic toxins is the Kt/V of urea, where K = the solute clearance, t = time over which the clearance is measured, and V = the volume of distribution of the solute or the total body water of the individual. Kt/V is usually measured by collecting the total dialysate drained in 24 hours. The daily clearance of urea, K = the total drain volume collected over these 24 hours multiplied by the ratio of the concentration of urea in the dialysate to the plasma concentration. An individual's residual kidney function can contribute significantly to their overall solute clearance. For this reason, both the Kt/V_{urea} from PD and the residual Kt/V_{urea} are measured to calculate the overall clearance achieved by a person on PD.

While Kt/V_{urea} is the most common method of measuring solute clearance, creatinine clearance has also been used. The daily creatinine clearance is similarly calculated by multiplying the total drain volume collected over these 24 hours multiplied by the ratio of the concentration of creatinine in the pooled dialysate to the plasma creatinine concentration. The daily residual creatinine clearance is also calculated from a 24-hour urine collection for people with residual kidney function.

Kt/V_{urea} and creatinine clearance will sometimes be discordant. This happens more often in people with considerable residual kidney function because residual creatinine clearance usually overestimates glomerular filtration rate since creatinine is not only filtered but also secreted in the tubules. On the other hand, residual Kt/V_{urea} underestimates the glomerular filtration rate since urea is reabsorbed in the tubules. In clinical practice, peritoneal Kt/V_{urea} and creatinine clearance are usually similar. Since creatinine is larger than urea, urea will be cleared more readily in shorter dwells. This difference in urea and creatinine clearance is usually only significant in the case of slow peritoneal solute transfer rate. Finally, weight will affect Kt/V to a larger extent than creatinine clearance if actual body weight is used instead of ideal body weight when calculating V. If actual body weight is used, V will be too low for patients with protein-energy wasting and too high for obese patients, resulting in Kt/V_{urea} estimates that are higher and lower, respectively, than creatinine clearance for the same patient.

It is important to note that while Kt/V_{urea} and creatinine clearance are useful estimates of small solute clearance, there is no target clearance that has been proven to improve an individual's health. These measurements should be used as one of several tools to assess the well-being of the person on PD. As the International Society of Peritoneal Dialysis stresses in the 2020 practice recommendations for prescribing high-quality goal-directed PD, the PD prescription does not need to be modified simply to reach a certain clearance target if the individual's symptoms, nutrition, and volume status are otherwise controlled.

Evaluating Increases in Serum Urea Concentration

Because measuring the Kt/V involves a 24-hour collection of the dialysate effluent as well as a 24-hour urine collection for those with residual kidney function, it is typically done, at most, on a quarterly basis. In practice, the serum concentration of urea or the blood urea nitrogen (BUN) level is used to follow trends in clearance in the shorter term.

When the BUN increases, it is either due to an increased production of urea or a decrease in clearance (Table 23.2). Increased production of urea can stem from an increase in the dietary intake of protein. Major gastrointestinal bleeding can also raise the concentration of urea as the blood is eventually metabolized to urea. Finally, hypercatabolic states can also increase urea production and can result from infection, inflammation, hyperthyroidism, metabolic acidosis, rhabdomyolysis, and use of glucocorticoids. One of the most common causes of a decrease in urea clearance is loss of residual kidney function. Nonadherence to the PD prescription can lead to a drop in solute clearance. Finally, a change in membrane function in either direction can lead to decreased clearance. A decrease in peritoneal solute transfer rate will reduce urea clearance if the PD prescription is comprised of shorter dwells. On the other hand, increases in peritoneal solute transfer rate can also decrease clearance if the prescription is for relatively longer dwells since ultrafiltration would decrease, decreasing clearance.

A thorough history and exam can usually differentiate between the different causes of increased urea production. A detailed diet history or food diary will usually reveal whether the person has been taking in significantly more protein than prior. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend that people on PD aim for a protein consumption of 1.2–1.3 g/kg body weight/day. Protein intake that is significantly higher than this may generate more urea than can be cleared by dialysis. There would be signs and symptoms of a major bleeding episode if a gastrointestinal bleed were increasing the BUN, as minor bleeds are unlikely to significantly raise the urea concentration. Causes of hypercatabolism are also usually obvious from the history and exam, and blood tests can be used to confirm the diagnosis. These might include a complete blood count or cultures to diagnose infection, TSH to check for hyperthyroidism, serum bicarbonate levels to look for metabolic acidosis, and creatinine kinase levels to confirm rhabdomyolysis.

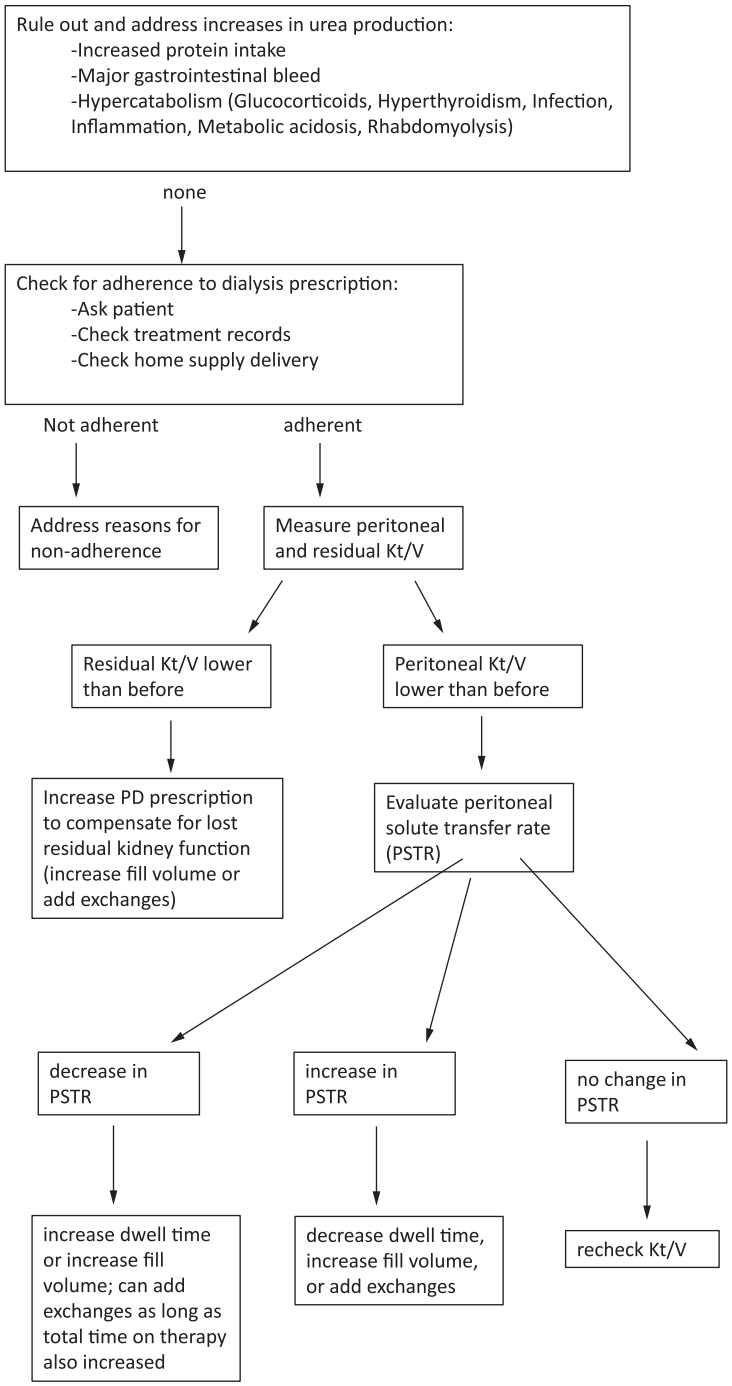
Assessing for decreases in urea clearance similarly involves a thorough history and usually will require further testing (Fig. 23.4). Providers can directly ask individuals if they have been able to complete all of their treatments. The amount of home dialysis supplies can also provide clues. If supplies are being delivered less frequently than expected or if there is a stockpile in the home, it is likely that the extra supplies are a result of skipped treatments. For those who are on automated PD, treatment records can also be reviewed to assess adherence. Formally measuring the peritoneal and residual Kt/V is almost always necessary to evaluate other causes for a drop in clearance. People on PD may report a decrease in urine output as a symptom of decreased residual kidney function. This would be confirmed by a lower residual Kt/V than prior measurements. If, on the other hand, the peritoneal Kt/V has dropped despite no change in the PD prescription, a PET should be performed to see how the peritoneal membrane function has changed as this will dictate how the PD prescription should be modified.

TABLE 23.2 Causes of Increased Blood Urea Nitrogen (BUN) Concentration

Increase in Urea Production	Decrease in Urea Clearance
Increased protein intake	Decreased residual kidney function
Major gastrointestinal bleed	Nonadherence to dialysis prescription
Hypercatabolism	Change in peritoneal membrane solute transfer rate (PSTR)
Glucocorticoids	
Hyperthyroidism	
Infection	
Inflammation	
Metabolic acidosis	
Rhabdomyolysis	

Modifying the Peritoneal Dialysis Prescription to Increase Solute Clearance

If nonadherence to the PD prescription is the heart of the issue, care should be taken to determine what aspects of PD are difficult for the person on PD to complete so that the prescription can be modified to fit their lifestyle and abilities. Using a cycler at night might decrease the burden of performing exchanges during the day. Having a dry period, especially during meals, or decreasing the fill volume for at least one exchange may minimize the bloating and discomfort that discourage some individuals from doing their exchanges. The person may need someone to assist them with performing dialysis, either temporarily as a respite or even long-term. Providers should also assess whether the psychosocial status of the individual may be interfering with their ability to perform their PD and offer support services, professional or peer based, as appropriate, to address these concerns.



• **Fig. 23.4** Evaluation and management of high blood urea nitrogen (*BUN*) concentration. Increases in BUN can be due to either increased urea production or decreased urea clearance. This algorithm presents a stepwise approach to the evaluation of high BUN. Kt/V_{urea} provides a measure of solute clearance by peritoneal dialysis. The Kt/V_{urea} is calculated from the daily peritoneal urea clearance (Kt), which is the product of the total 24-hour peritoneal drain volume and the ratio of urea concentration in the pooled drained dialysate to plasma. *V* is the volume of distribution of urea, which is 60% of ideal body weight in men and 55% ideal body weight in women. 24-hour urea clearance provides a measure of solute clearance by residual renal function. The 24-hour urea clearance per day is equal to [urine urea (mg/dL) × urine volume (mL)]/plasma urea (mg/dL) × 1440 minutes/day. ¶The severity of acidosis required to increase catabolic rate is not known. We generally target serum bicarbonate > 22 mEq/L. ΔThe peritoneal equilibration test (*PET*) characterizes peritoneal solute transfer rate (PSTR) and ultrafiltration across the peritoneal membrane. The PET is used to classify membrane function in order to optimize the dialysis prescription. Since PSTR can change over time, the PET is also used as a diagnostic test to identify causes of reduced solute clearance. ◊Occasionally, a cause for increasing BUN is not found. In such circumstances, it is important to assess the overall patient. If there is no evidence of uremia and declining nutrition and peritoneal dialysis is otherwise going well, many clinicians would just continue peritoneal dialysis as is. (Adapted from Burkart JM. Inadequate solute clearance in peritoneal dialysis. Uptodate. Topic 1973, Version 24.0.)

If a person's residual kidney function has dropped, there are several ways to increase the dialysis prescription to make up for this lost clearance. An increase in the fill volume or number of exchanges will increase the dialysis that is delivered. As with all changes in prescription, this should be discussed with the person on PD and tailored to meet their needs. Many individuals can tolerate a 500-mL increase in the fill volume, especially if they are on a cycler overnight. This would avoid increasing the time on therapy. For those who have only been on a cycler overnight and are dry during the day, adding a last fill during the day may be most convenient. If they already have a last-day fill, an additional days exchange would be a reasonable next step for increasing the prescription.

For people whose peritoneal Kt/V has dropped, a PET should be performed. If the peritoneal solute transfer rate has increased compared to prior, the dwell times should be shortened. This will prevent the dialysate from being reabsorbed and thereby increase clearance. Patients who have been on continuous ambulatory PD (CAPD) often benefit from transitioning to automated PD, as exchanges done on a cycler are shorter than the 4–6 hours typical of CAPD. Meticulous management of the long day dwell is imperative, and it may require two day-time exchanges with dextrose-based solutions or icodextrin. The volume of the exchanges can also be increased. The increased total volume of dialysate will increase clearance, and the increase in the volume of each individual exchange increases the time it takes for the solutes to equilibrate, allowing for diffusion to continue over a longer period of time. If the individual is already on shorter dwells, additional exchanges can be added to increase the dose of dialysis.

A different approach should be taken if the peritoneal solute transfer rate has decreased from before. An increase in fill volumes will also increase solute clearance. However, the dwell time should not be shortened; longer dwell times would be preferable. Additional exchanges will also increase clearance, but only if the total time on therapy is also increased. If more exchanges are done over the same period of time, the actual time for diffusive clearance will decrease, which would make the Kt/V even lower.

Finally, if the PET shows that there has been no change in the peritoneal solute transfer rate, the peritoneal Kt/V should be remeasured to see if it really had decreased from prior. Particular attention should be paid as to whether the samples were correctly collected.

Suggested Reading

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Volume Management With Peritoneal Dialysis

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Introduction

Among patients receiving kidney replacement therapy, it is well established that persistent volume overload is associated with higher mortality. In peritoneal dialysis (PD) patients specifically, the Initiative of Patient Outcomes in Peritoneal Dialysis (IPOD-PD) study is a large prospective observational study of 1092 incident PD patients across 32 countries that assessed hydration and nutrition status at dialysis start and every 3 months with bioimpedance analysis (BIA). The IPOD-PD study demonstrated that by BIA measurement, only 38.7% of patients were euvolemic at baseline. In an observational follow-up study of the IPOD-PD, Van Biesen et al. found that volume overload as measured by BIA was associated with higher mortality and hospitalization rates. It has been postulated that persistent fluid overload may lead to impairments in left ventricular cardiac geometry, which has been associated with a higher mortality risk among patients receiving kidney replacement therapy. Volume overload is also frequent in prevalent PD patients, as demonstrated by The European Body Composition Monitoring (EuroBCM) study, which examined a cross-sectional cohort of 639 prevalent PD patients across six European countries. EuroBCM demonstrated that 54.3% of prevalent PD patients were volume overloaded as measured by BIA. Given these findings, and that cardiovascular disease is the primary cause of mortality in patients receiving kidney replacement therapy, fluid and volume management has been highlighted as an integral component of care for patients receiving PD in the most recent International Society for PD (ISPD) Cardiovascular and Metabolic guidelines.

Interestingly, in IPOD-PD, there was significant disagreement between volume status as assessed by BIA and that assessed via clinical exam. Further complicating the assessment of volume status is the presence of "fluid compartment disorders," such as hypoalbuminemia, cardiac dysfunction, or liver disease, all of which are common in PD patients. These patients may present with increases in extracellular fluid volume (as assessed by BIA) in the presence of normal or reduced intravascular volume. This makes therapeutic goals for fluid and sodium removal challenging, based on discordant volume status assessments between the intravascular and extracellular fluid compartments. This was highlighted by John et al., who examined a cross-sectional cohort of 46 PD patients and demonstrated that while hypoalbuminemia was associated with an increase in extracellular fluid volume to total body water ratio as measured by BIA, this was not accompanied by an increase in plasma volume (as measured by ^{125}I-labeled albumin dilution). The interpretation of multiple clinical exam findings and investigations of volume status together in the context of patient comorbid conditions is crucial in evaluating the PD patient. This assessment needs to be individualized considering patient-specific risks of excess fluid accumulation or loss. For example, in the presence of significant cardiac dysfunction, there may be some degree of "permissive edema" in an effort to preserve intravascular fluid volume and avoid the consequences of hypovolemia, including a more rapid decline in residual kidney function (RKF), syncopal episodes, hypotension and falls, and even heightened mortality risk. On the contrary, there are no data to suggest that patients should be kept intentionally overhydrated in an effort to preserve RKF. This was demonstrated by McCafferty et al. in a retrospective review of volume status in a cohort of 237 PD patients split on the basis of hydration tertiles (low, middle, high), and no significant correlation between hydration status and the decline in RKF was shown. It should be noted that this study was observational, and therefore, hydration status was not an active intervention and may have been the result of comorbid conditions such as impaired cardiac function that may have impacted the relationship between hydration status and RKF decline.

Taken together, "optimal volume status" in PD is a concept that likely resides in a narrow therapeutic window and remains a constant push/pull between the threats of hypovolemia and those of extracellular fluid volume expansion, namely, increased blood pressure (BP) and derangements in left ventricular geometry. The impact of these threats likely varies between individuals, thereby requiring a

personalized approach. In this chapter, we will review multiple tools that can be used to assess the volume status of PD patients, as well as highlight an approach to sodium and water removal among patients receiving PD, emphasizing both dialytic and nondialytic strategies and considering the unique situations of the acutely volume overloaded and anuric patient.

Fluid Status Exam

Physical Exam

Frequent and routine volume assessment among patients receiving PD remains a cornerstone of providing high-quality care. Physical exam maneuvers can yield clues to the volume status of the patient; however, volume assessment remains imprecise and suffers from interobserver variability. These maneuvers include BP assessment (postural if needed), weight, peripheral edema, rales on lung auscultation, third heart sound on cardiac evaluation, and jugular venous pressure (JVP). None of these features alone is enough to determine volume status, and multiple signs and investigations together should be used to determine the volume status of patients.

Assessment of BP is a key parameter for PD patients, as volume overload underlies an important mechanism for hypertension in dialysis patients. In hemodialysis (HD) patients, Dry-weight Reduction in Hypertensive Hemodialysis Patients (DRIP): A Randomized, Controlled Trial demonstrated that a reduction in dry weight was associated with improvements in BP control among hypertensive HD patients. In PD patients, similar findings were demonstrated by Gunal et al. in a small single-center study of 46 PD patients with hypertension, in whom they discontinued BP medications and studied the effects of sodium restriction and enhanced ultrafiltration (UF) (using 4.25% [3.86% anhydrous] solution) on BP; they found that with strict sodium restriction and aggressive UF, there was a significant decrease in BP, a decline in patient weight, and decreased cardiothoracic index (a marker of cardiomegaly, measured on chest x-ray). There is paucity of literature examining the ideal target BP in PD patients; thus, BP goals are largely extrapolated from general population data. As per the Kidney Disease Improving Global Outcomes (KDIGO) Hypertension in CKD Guidelines, both diabetic and nondiabetic patients with albuminuria greater than 30 mg/24 hours should target BP < 130/80 mm Hg, while those without albuminuria (less than 30 mg/24 hours) should target BP < 140/90 mm Hg regardless of diabetic status. In the recent KDIGO Controversies Conference on Hypertension and Volume Management in Dialysis, many of the difficulties with BP management in those receiving kidney replacement therapy were reviewed. Particularly, it is unclear what BP targets should be employed for patients receiving dialysis with cardiovascular disease as they have been largely excluded from many studies yet constitute a large segment of HD and PD populations. A recent large observational cohort study of 7335 incident PD patients in the Zhejiang Renal Data System in China evaluated the average BP over the first 3 months of therapy and its association to all-cause mortality and cardiovascular mortality. They found a U-shaped curve, with both hypertension (systolic BP > 141 mm Hg, diastolic BP > 85 mm Hg, mean arterial pressure [MAP] > 102 mm Hg, and pulse pressure > 60 mm Hg) and hypotension (systolic BP < 119 mm Hg, diastolic BP < 67 mm Hg, MAP < 88 mm Hg) being associated with higher all-cause mortality. While this study provides insights on the association with early BP abnormalities in PD patients, it did not encompass longitudinal changes in BP and antihypertensive therapy that may have modified the association between BP and mortality. Even the appropriate method to measure BP is unclear for PD patients; in the HD population, it has been identified that the best means to measure BP is home 44-hour ambulatory monitoring. If ambulatory BP monitoring is unavailable due to resource limitation or adherence by the patient, home BP measurements would be the next preferred modality, followed by in-office measurements, and finally, predialysis and postdialysis measurements being the least useful. There have been no studies assessing out-of-unit BP monitoring in PD patients. Given the paucity of data, it can be extrapolated from HD literature that in those receiving PD, ambulatory or home BP measurements would be the preferred method and, by virtue of the autonomous nature of the therapy, should be readily available as part of routine clinical care and aided by the emergence of remote patient monitoring technologies.

Weight should be routinely followed, as excessive weight gain on PD can be a sign of fluid retention and has been associated with worse outcomes. It is important to follow weight longitudinally, as a single measurement is not helpful, but serial values can yield insight into daily variations in volume status. There are inaccuracies that can occur with weight if not measured appropriately. Patients should weigh themselves on the same scale at the same time of day with minimal clothing to avoid inaccuracies in weight measurement. In the established PD patient, daily weights can be a useful tool to assess and manage volume status.

Additional methods of volume assessment can be used to supplement the physical examination. BIA, lung water, and inferior vena cava (IVC) ultrasound (US) are all tools that can help one further delineate the volume status of patients, and biomarkers including B-type naturetic peptide (BNP) and N-terminal fragment of the precursor proBNP (NT-proBNP) can also be used to evaluate volume status.

Bioelectric Impedance Analysis

BIA is used to assess the total body water, extracellular body water, and intracellular body water of a patient; it is a safe, economical, and portable means of assessment. Using low-voltage electrical currents determines the fluid composition of body compartments and thus has been of interest as a means to better assess volume status. The technique,

however, has its limitations, including lower accuracy in women, pregnant patients, and those with pacemakers, and is affected by significant obesity, protein energy wasting, and prior limb amputations. Multiple groups have investigated the prognostic significance of BIA derangements in dialysis patients (including the IPOD-PD and EuroBCM studies described earlier), and generally, it is accepted that BIA provides a reasonably accurate assessment of hydration and lean body mass; however, care in interpretation must be taken as multiple factors can affect this measurement. Such factors include the nutritional health of patients, as protein-energy wasting results in a loss of fat and muscle and a relative overhydration on BIA. It is unclear if correcting this relative overhydration in those with protein-energy wasting is of clinical benefit, and it has not been established if correction would lead to deleterious effects on RKF. Furthermore, BIA does measure extracellular fluid volume but does not provide a measure of intravascular volume, which may pose a challenge to distinguish among those patients who may have extracellular fluid volume expansion yet normal or reduced intravascular volume versus patients with increases in both extracellular and intravascular volume. There have been very limited studies including PD patients and, within these studies, there is heterogeneity of patients with respect to levels of RKF. In a systematic review, the use of BIA as part of routine clinical care has not been shown to improve mortality in PD patients, although it does lead to higher rates of extracellular water decline when used routinely in follow-up. One would then postulate if extracellular water decline occurs that there would be a positive effect on BP control with use of BIA; however, the data at this time are conflicting. A single-center randomized control trial (RCT) of 240 patients by Tian et al. compared volume status management guided by traditional clinical exam methods versus BIA and showed improvement in fluid management over the short-term with BIA, but no significant improvements in BP, mortality, or technique survival. However, a prior systematic review by Covic et al. that included seven RCTs encompassing 1312 patients similarly found that BIA did not have significant improvement in mortality for PD patients, but the use of BIA did improve systolic BP control. Very few of these studies used mortality as an outcome for BIA and were underpowered to achieve realistic and modest differences in mortality risks. The Effect of Bioimpedance and Vitamin D versus Usual care on left ventricular mass in PD patients (FLUID study) is a multicenter RCT across sites in Canada that is evaluating the role of BIA-guided fluid management versus standard of care on left ventricular mass as measured by cardiac magnetic resonance imaging (MRI), the results of which should be imminently forthcoming. Currently, while BIA may have some clinical value in assessing hydration status, its utility for reduction in mortality and BP is uncertain in PD patients. BIA should be used with caution and only as an adjunct to the clinical exam to establish a volume status and may be helpful to quantify volume removal targets for the patient, but its role remains controversial given the findings presented earlier.

Lung Water Ultrasound

Lung water evaluation for extravascular water has been well studied and is an established method to evaluate for pulmonary congestion in patients on dialysis. Studies of lung US in PD patients show that a high percentage of patients (46%) have lung congestion. US of the lungs should include multiple windows in different planes (midclavicular, anterior axillary, midaxillary). Confirmation of three or more B-Lines (white "comet tails" arising from the pleural line continuing to the bottom of the screen) in two or more bilateral lung zones is considered pathological and suggests increased fluid in the lungs. Supportive data exist in the HD population for the use of lung US in fluid management; however, there is a paucity of such data in PD patients. A recent RCT by Loutradis et al. showed that compared to standard clinical assessment, use of lung US-guided UF resulted in a reduction in BP and greater dry weight reduction in HD patients. It is important to remember that other pathological findings, such as lung fibrosis or consolidation, will also produce B-Lines, and these results need to be interpreted in the clinical context of the patient. Furthermore, B-Lines only assess for extracellular lung water and do not provide an assessment of intravascular volume status, which limits diagnostic utility in patients with fluid compartment disorders.

Inferior Vena Cava Ultrasound

IVC measurements include the diameter of the IVC expressed as an index of body surface area (IVC index, units mm/m^2) and collapsibility index (maximal diameter on expiration minus minimal diameter on deep inspiration) divided by maximal diameter on expiration, with diameters measured at 3 cm from the right atrium. IVC measurements can be used to assess for both volume overload and fluid responsiveness (as defined as an increase in stroke volume of 10%–15% after a 500 mL bolus of crystalloid over 10–15 minutes, indicating possible volume depletion) and have been shown as a useful tool in assessment of dry weight for HD patients. Generally, an IVC collapsibility index of less than 50% indicates fluid responsiveness, whereas an index greater than 75% indicates volume overload. There are limited data for the use of IVC measurements in PD patients; however, Toprak et al. assessed IVC measurement in 69 continuous ambulatory PD (CAPD) patients and found that it was independently predictive of left ventricular geometry; specifically, volume overload is known to be associated with left ventricular dilation and eccentric left ventricular hypertrophy, and IVC dilation on US was seen to be predictive of eccentric left ventricular hypertrophy geometry. Of course, there are multiple drawbacks to IVC measurement, most notably that it is a measurement of increased right atrial pressures and is not directly a measurement of volume status; thus, increased IVC index and collapsibility index can be seen in any condition that increases right atrial pressures (e.g., heart failure, pulmonary hypertension)

or any condition that leads to the development of tricuspid regurgitation (e.g., pulmonary hypertension, heart failure, or coronary artery disease). Finally, the IVC is susceptible to anything that causes changes in intrathoracic pressure, and there is significant interuser variability in IVC measurements; thus, this technique should only be used by experienced operators and interpreted in the context of the patient's other comorbidities.

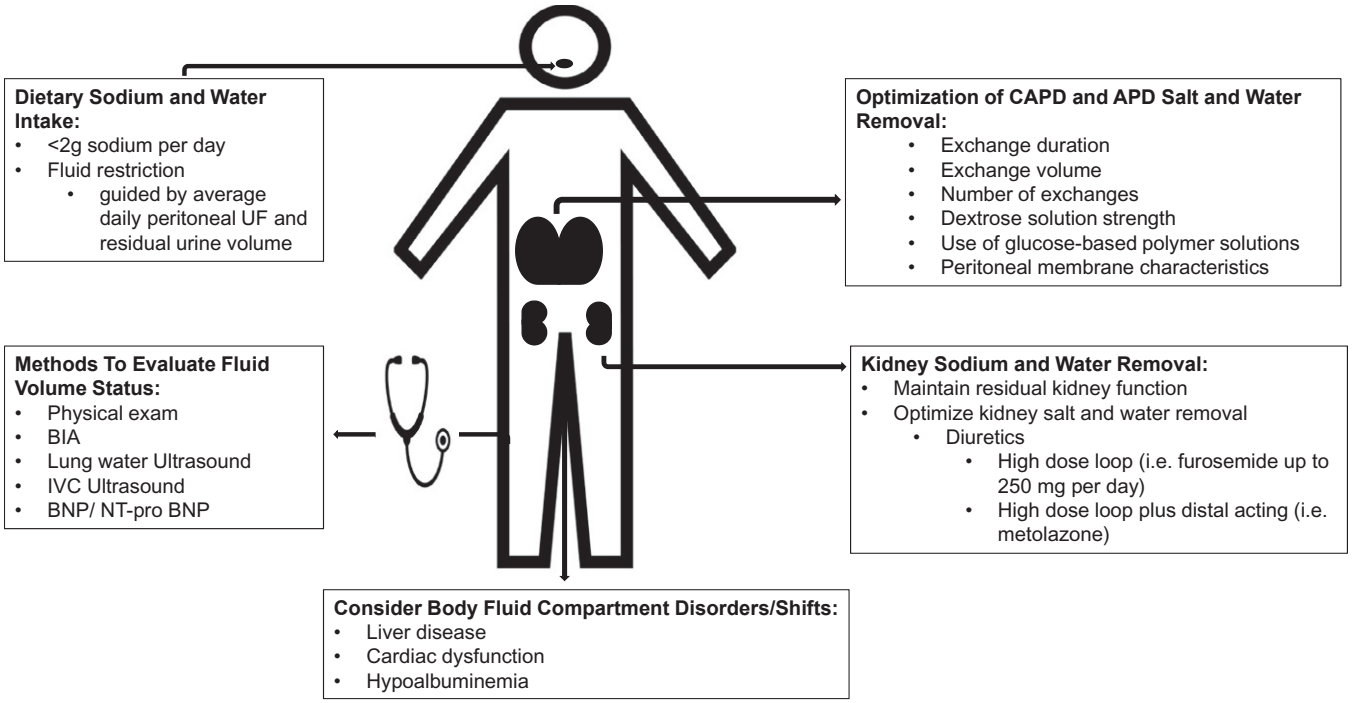
Biochemical Markers of Volume Overload

BNP is primarily secreted by the ventricular myocardium but can also be expressed from other tissues, including the brain, adrenal glands, kidneys, and lungs. Transcription of BNP occurs under pathophysiologic stressors, including stretch or strain of the myocardium occurring due to pressure or volume overload, as well as other factors including ischemia, proinflammatory cytokines, sympathetic overactivity, and vasoactive peptides. The physiologic roles of BNP include inducing diuresis, peripheral vasodilatation, and inhibition of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system. The NT-proBNP is often now used in place of BNP measurement due to its longer half-life (120 minutes compared with 20 minutes for BNP). Both BNP and NT-proBNP are found to be elevated in patients with reduced kidney function, and this is felt to be secondary to both increased production due to the high frequency of ventricular dysfunction and left ventricular hypertrophy in the dialysis population and decreased clearance of the peptide. Thus, a single measurement in PD patients is often not of significant diagnostic utility. While it is well established that both BNP and NT-proBNP are cleared by HD, there is a paucity of literature regarding the clearance of PD. One small study of 11 PD patients by Obineche et al. examined serum BNP and NT-proBNP levels present in PD patients before, during, and after nightly intermittent PD (NIPD) treatment and found that PD had no effect on the concentration of these peptides in the serum. However, its utility may be a serial marker, as changes in BNP and NT-proBNP levels correlate with volume status; increases correlate with worsening volume overload and reduction of BNP and NT-proBNP, as associated with improvement in overhydration measurements in the PD-specific bioimpedance literature. Ultimately, longitudinal BNP and NT-proBNP measurements in PD patients may be helpful to assess changes in volume status, but interpretation is complicated by a number of factors, including known higher baseline values in dialysis patients, multiple stimuli for secretion in dialysis patients, unclear knowledge of the role of peritoneal clearance, and the impact of cardiovascular comorbidities on their interpretation.

Left Ventricular Mass

Left ventricular mass increases or hypertrophy is commonly seen in dialysis patients and present in up to 74% of incident dialysis patients. Multiple factors contribute to the development of left ventricular hypertrophy, including anemia, hypertension, volume overload, and disorders of bone mineral metabolism. There are multiple different ways to assess for left ventricular hypertrophy, including electrocardiogram (ECG), echocardiography, and MRI. Electrical diagnosis with ECG has largely been replaced with anatomical measures such as MRI and echocardiogram due to the low sensitivity of ECG for detection of left ventricular hypertrophy. An echocardiogram is generally considered the gold standard for diagnosis of left ventricular hypertrophy in hypertensive disease; however, the 2017 American Heart Association Hypertension guidelines do not discuss preference of echocardiography over MRI, and MRI has been shown to be an efficacious and useful tool for identifying left ventricular hypertrophy in centers that have access to this imaging modality. The advantages of MRI include being more reproducible than echocardiogram, better assessment of diastolic dysfunction and atrial volumes, and does not rely on geometric assumptions like echocardiography does. However, the pitfalls include a long exam time; limited availability and expertise, particularly in resource-poor settings; high cost; and an inability to perform the exam in patients with metallic implants. Echocardiography, while widely available, has limitations when evaluating left ventricular hypertrophy, including high interobserver and interstudy variability and assessment of diastolic dysfunction (one of the first complications of hypertension) changes with heart rate and preload variability, significantly affecting measurements. Ultimately, given the lack of availability for MRI, generally, echocardiography is the investigation of choice for left ventricular hypertrophy, and MRI is reserved for those cases where there is discrepancy between ECG and echocardiogram, severely progressive left ventricular hypertrophy, inconclusive echocardiogram, or in evaluation of hypertrophic cardiomyopathy. Left ventricular hypertrophy has been used as a surrogate for cardiovascular outcomes in patients with kidney disease, and as such, reductions in left ventricular hypertrophy are an endpoint for many trials in patients with chronic kidney disease (CKD). This use stemmed from the Heart Outcomes Prevention Evaluation (HOPE) and Losartan Intervention For Endpoint reduction in cardiovascular morbidity and mortality (LIFE) trials, which established that interventions that lead to regression of left ventricular hypertrophy are associated with lower cardiovascular mortality, myocardial infarction, stroke, and heart failure in patients with essential hypertension. However, in a systematic review and meta-analysis by Badve et al., 73 trials that used the change in left ventricular hypertrophy as an outcome found that there is no consistent correlation between intervention-induced reduction in left ventricular hypertrophy and mortality in CKD patients. Taken together, whether or not left ventricular hypertrophy is a direct consequence of fluid overload in PD patients or a therapeutic target for reduction in extracellular fluid volume remains unclear.

Volume status assessment remains a complex issue for patients on dialysis, and despite advances with US, BIA, and left ventricular hypertrophy, subjective clinical assessment still remains the standard of care for volume assessment in



• **Fig. 24.1** This Summative Figure Reviews the Complexity of Fluid Management, Including Mechanisms of Fluid Accumulation, Fluid Shifts, and Fluid Removal. The management of fluid disorders can be achieved via dialytic and nondialytic mechanisms. Examination techniques to assess volume status in the intravascular and extravascular compartments and techniques to increase sodium and fluid removal via the peritoneum or the kidney in peritoneal dialysis patients. *APD*, Automated peritoneal dialysis; *BIA*, bioimpedance analysis; *BNP*, B-naturetic peptide; *CAPD*, continuous ambulatory peritoneal dialysis; *IVC*, inferior vena cava; *LVH*, left ventricular hypertrophy; *NT-proBNP*, N-terminal pro-B-naturetic peptide.

patients receiving kidney replacement therapy, and use of these additional tools has not been shown to affect mortality. See Fig. 24.1 for a summative graphic description of volume assessment in PD patients.

Nondialytic Management of Sodium and Water Handling

Dietary Management of Sodium and Water

Dietary sodium restriction is a cornerstone of therapy for all dialysis patients. A myth in PD is that compared to patients receiving facility-based HD, those on PD can liberalize their sodium and fluid intake; however, dietary management needs to be tailored to the individual patient, and liberalization can often lead to volume overload. Episodes of fluid overload are significantly more common in patients who do not adhere to sodium and fluid restriction as compared to patients who are adherent to dietary sodium and water restrictions, and dietary nonadherence is an independent risk factor for symptomatic fluid gain. The ISPD Cardiovascular and Metabolic guidelines suggest that sodium intake should be less than 2 g/day or less than 5 g sodium chloride per day. While specific data for sodium and fluid restriction in PD patients are limited, recommendations are extrapolated from general population data (Cochrane review) and data in the HD and CKD populations. Low sodium intake has shown to reduce BP and is associated with reduced stroke and cardiovascular mortality in the general population. Sodium restriction in PD patients is an important therapeutic intervention to maintain optimal volume status, and inability to adequately manage sodium and fluid is associated with mortality. Dietary restriction has proven to be difficult for many patients, with wide ranges of adherence seen, from 10% to 60% of patients depending on the study. Factors such as lifestyle impact adherence as restrictive diets can isolate patients from family and friends on top of the isolation that occurs due to their chronic illness. In a study by Clark-Cutaia et al., female gender and younger age were identified as being associated with poor adherence to dietary sodium restriction. It is important to individualize dietary recommendations for PD patients as some patients who may be prone to volume depletion should avoid sodium and fluid restriction. Regular review with a dietician can help ensure that patients adhere to the prescribed diet, improve their sodium literacy, and allow for individualization of a diet plan taking into account cultural considerations. Particularly, engaging the patient in education regarding the importance of fluid and sodium restriction improves adherence to a prescribed diet as well; using motivational interviewing with frequent follow-up improves adherence with dietary restriction in patients with kidney disease. Fluid intake allowance is highly variable between patients and should be modeled off their usual fluid removal in a 24-hour period (residual urine output plus UF) once a desired body weight has been

established. It is important to regularly assess residual urine volume and adjust fluid restrictions accordingly. Finally, for patients who either are unable to adhere to sodium and fluid restriction or, despite adherence, are still volume overloaded; sodium and water removal must be enhanced by either increasing urinary sodium and volume removal or by modifying the PD prescription to increase peritoneal sodium removal and UF.

Role of Residual Kidney Function

In patients receiving dialysis, RKF has been identified from observational studies as an important factor providing multiple purported benefits to the patient: lower mortality, longevity of technique, and better quality of life. Additional benefits of RKF include better nutritional status and enhanced middle molecule and phosphate clearance. RKF contributes to both fluid and sodium removal; this contribution to clearance is significantly associated with survival. The importance of RKF was highlighted in the Canada–USA (CANUSA) study, a prospective cohort study including 680 PD patients in the United States and Canada, and demonstrated that RKF, particularly urine volume over urinary solute clearance, was strongly associated with overall survival, technique survival, and fewer hospitalized days. The association of RKF with survival may be related to its important role in maintaining volume status in patients receiving PD. RKF is associated with lower BP, lower left ventricular mass, and lower extracellular fluid volume status in patients receiving PD. Compared with their conventional HD counterparts, RKF is persevered for a longer period among PD patients. Modifiable risk factors to preserve RKF and urine volume are an important part of PD therapy. Factors that contribute to preserving RKF among patients receiving PD include avoidance of hypovolemia and nephrotoxic medications (nonsteroidal anti-inflammatory drugs [NSAIDs], iodinated contrast), RAAS blockade, preferential use of neutral-pH, low–glucose degradation product (GDP) dialysate solutions, and avoidance of extracellular fluid volume depletion. Ultimately, preservation of RKF is highly important in PD patients, providing a metabolically neutral means to maximize sodium and water excretion as opposed to peritoneal sodium and water removal, which often requires increasing use of hypertonic dextrose, leading to enhanced glucose absorption and the metabolic consequences that ensue.

Strategies to Enhance Renal Sodium and Water Removal

Diuretics are commonly used in PD patients to facilitate fluid removal and increase urine volume. Diuretics can successfully maintain euvolemia in patients with greater than 100 mL per day of urine. It is well established that use of loop diuretics results in increased urine volume. This has been verified by Van Olden et al., who studied the effects of high-dose furosemide on CAPD patients; they found that high-dose furosemide (2 g dose) increased urine volume and fractional excretion of sodium and potassium, with no effect on fractional excretion of urea or electrolyte free water, and no effect on glomerular filtration rate over a 24-hour clearance period. Loop diuretics are not only beneficial for PD patients; in a recent retrospective, observational study by Sibbel et al., the benefit of loop diuretics in incident HD patients was examined. They found that continuation of loop diuretics was associated with significantly lower all-cause hospitalization, less intradialytic weight gain, and less intradialytic hypotension. While no RCT evidence exists, this observational study shows promise that there may be benefits from continuing diuretics in all incident dialysis patients who have some degree of RKF. If, despite high-dose loop diuretics, increased urinary volume is needed, distal-convoluted tubule acting diuretics (such as metolazone) can be added for synergistic effect as chronic loop diuretic use has been shown to lead to distal convoluted tubule hypertrophy and is a cause of diuretic resistance. A recent small single-center RCT in Thailand compared control single-diuretic high-dose furosemide (1000 mg per day) to an intervention group, which received triple high-dose diuretic (furosemide 1000 mg, spironolactone 50 mg, and hydrochlorothiazide 100 mg daily) and demonstrated a sustained increase in urine volume and decrease in overhydration measured by BIA at 6 months with no increase in adverse events in the triple diuretic group as compared to control. However, no significant differences in BP or sodium removal were seen. The use of high-dose loop diuretics is a promising strategy in the future to maintain urine volume in PD patients; however, adoption of this strategy has been slow, particularly given that many physicians do not have clinical experience with such high-dose diuretics, which may limit the widespread uptake of this approach (previous studies used standard furosemide doses of 250 mg per day). It is important to be cognizant of the adverse effects of diuretics and monitor patients, particularly at the time of initiation. Ototoxicity from loop diuretics remains a major concern but is typically described in the literature primarily with intravenous administration over oral dosing. Increasingly, aldosterone inhibitors have been studied for possible protective effects in dialysis patients, with evidence to suggest their use to be associated with lower cardiovascular mortality, and use shows evidence of reduced inflammation and fibrosis of the peritoneal membrane in animal models; however, the concerning side effect limiting their use is hyperkalemia, which is less concerning in PD patients as they typically do not have as frequent hyperkalemia as their HD counterparts. Lin et al. examined the use of low-dose spironolactone in dialysis patients in a 2-year RCT of 253 dialysis patients (both HD and PD), noting reduction in cardiovascular and cerebrovascular death in the spironolactone cohort. Currently, a Cochrane review is underway to better understand the benefits and risks of aldosterone antagonists, and more evidence is needed in PD to assess their impact on enhancing diuresis, preserving RKF, and cardiovascular mortality. Diuretics are an integral component of fluid management in PD patients and should be considered in any patient with residual urine output greater than 100 mL/day, and high doses of diuretics should be

considered with possible distal diuretics once maximal doses of loop diuretics have been used and additional urinary sodium and water removal are required. Aldosterone receptor antagonists may show promise in reducing the cardiovascular morbidity of patients receiving PD.

Determination of Peritoneal Sodium and Water Removal

Peritoneal removal of sodium and water in PD occurs by unique mechanisms. Sodium removal is achieved by both diffusion of sodium down its concentration gradient and convective clearance. The convection and diffusion of sodium (and other small solutes) have been postulated to occur in the context of the "three-pore" kinetic model of water and solute movement across the peritoneal membrane, in which the peritoneum is purported to consist of large, small, and ultrasmall pores (water-only-aquaporins) through which solutes (small and large pores) and water (all three pores) move across the peritoneal membrane. Fluid removal in PD occurs largely via an osmotic pressure gradient created by an osmotic agent instilled in the PD fluid (dextrose or non–dextrose based) that translates into a transperitoneal pressure gradient that serves as the driving force for fluid movement across the peritoneal membrane.

Factors related to the PD prescription that impact fluid and sodium removal include the dwell volume of dialysate instilled, the number of exchanges, their duration, the tonicity of the dialysate, and the osmotic agent used. Each of these factors contributes to both sodium and water removal and is discussed here. Individual patient characteristics, particularly peritoneal membrane surface area, solute peritoneal membrane characteristics, and the osmotic conductance of the peritoneal membrane to dextrose also play major roles in how the previous prescription-related factors influence sodium and water removal within an individual.

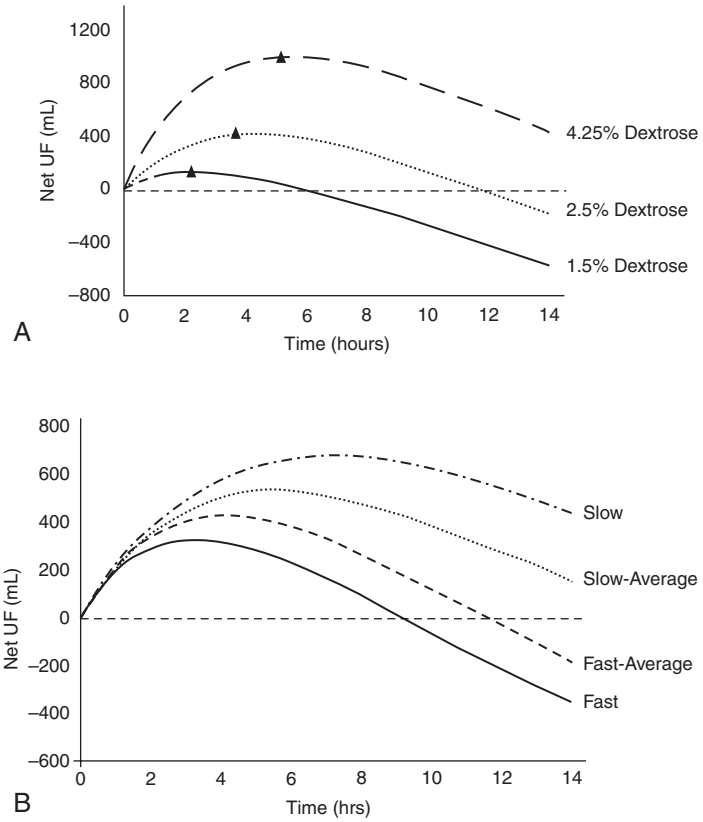
a) *Dwell volume:* Increasing dwell volumes allow for more of the peritoneal membrane to be in contact with dialysate, thus facilitating more transfer of solute and water. However, if dwell volumes are too high, there is a concern that increases in intra-abdominal pressure may oppose the transperitoneal osmotic forces that largely drive peritoneal UF; this was demonstrated in a small report, but the overall clinical significance of this remains unclear. In adults, dwell volumes are typically between 1 L and 2.5 L and do not routinely exceed 3 L due to increasing risk of complications with patient discomfort (i.e., back pain), leaks, hernias, and other risks related to increased intraperitoneal pressure. Dwell volumes for individual patients are guided by body habitus (larger volume for larger patients). This is best highlighted in the pediatric PD literature, where fill volume is more precisely determined by body surface area in mL/m^2 and intraperitoneal pressure is monitored.

b) *Dwell duration:* The length of the dwell is important and needs to be considered in the context of peritoneal small solute transfer characteristics. The highest osmotic gradient for UF is at the beginning of the PD dwell, where dextrose concentrations are highest, and as the dextrose is absorbed, the gradient dissipates. The time at which maximal UF is achieved is referred to as osmotic equilibrium and is different for each solution (Fig. 24.2A). As such, dwell times that are longer may result in less UF and even reabsorption of fluid if long enough time period has elapsed, while shorter dwells may have failed to reach the point of maximal UF. The determination of ideal dwell length to maximize fluid removal needs to be individualized in the context of a patient's peritoneal membrane characteristics.

c) *Dextrose strength:* The most common commercially available dextrose solutions are 1.5% (1.36% anhydrous), 2.5% (2.27%), and 4.25% (3.86%) solutions. There is limited availability of a 0.5% solution in certain countries, which will result in fluid reabsorption from the onset of the dwell. It is important to appreciate the maximum UF that can be achieved by the solutions, as shown in Table 24.1, which plays an important role in terms of the duration of dwells that should be prescribed. These "maximum UF" measures may also vary based on peritoneal membrane characteristics and diminish with reductions in osmotic conductance to glucose, which may occur over time in patients receiving PD. Higher-concentration dextrose solutions exert more osmotic pressure and thus can achieve higher fluid removal and should be a strategy in the acutely volume overloaded patients; however, this is at the cost of exposure to higher glucose concentrations, which may have negative metabolic consequences and may be deleterious to the peritoneal membrane over time.

d) *Peritoneal membrane characteristics:* Within the first few months of PD (but after 6 weeks), each patient undergoes a peritoneal equilibrium test (PET), which evaluates the speed with which dextrose is absorbed across the membrane; a standard PET uses 2 L of 2.5% dextrose solution over 4 hours. The PET classifies patients into one of four categories: low, low-average, high-average, and high peritoneal solute transfer rates (PSTR), as shown in Fig. 24.2B. Those who retain intraperitoneal dextrose for a longer period of time (slow PSTR) and experience slower dextrose absorption will have enhanced UF and will have a longer time to fluid resorption. This is in contrast to people with fast PSTRs, who dissipate the dextrose gradient much faster, and while they often have rapid diffusive solute clearance, they have limited convective clearance due to the loss of osmotic force for UF. Observational studies have shown that people with fast PSTRs may experience more volume overload; however, there is no consistent association between PSTR and higher mortality, particularly in the era of increasing use of automated PD (APD) (discussed later).

e) *Solution type:* The most widely used dialysis solutions are conventional glucose-based, lactate buffered, low-pH solutions; however, it is important to note that other commercially available solutions are available in some parts of the world, including amino acid-based solutions; low-GDP, neutral-pH solutions; and icodextrin.



• **Fig. 24.2** (A) Ultrafiltration *(UF)* achieved for standard peritoneal dialysis dialysate over time. A longer duration of dwell past osmotic equilibrium (▲ for each solution) results in decreased net UF. Allowing the dialysate to dwell for excessive periods of time can result in negative UF. (B) UF variability seen for different peritoneal membrane solute transfer rates, with a 2 L 2.5% dextrose. Patients with fast peritoneal solute transfer rates achieve lower maximal UF and have a shorter time to fluid reabsorption. (A, adapted from Advanced Renal Education Program and used with permission.)

TABLE 24.1 Maximal UF and Peak Times for UF for Differing Dextrose-Based Dialysate and Icodextrin

Solution	Peak UF time	Maximum UF Volume (mL)
1.5% dextrose	140 minutes	330 ± 187
2.5% dextrose	240 minutes	650
4.25% dextrose	247 minutes	1028 ± 258
7.5% Icodextrin	10 hours	351 ± 250

UF, Ultrafiltration.

Low-Glucose Degradation Product Solutions

Low-GDP solutions are buffered with lactate or bicarbonate and have a more physiologic pH when compared to conventional solutions; however, the composition of the solutions and total GDP level vary depending on the manufacturer. Minimizing the GDP content of PD solutions may be beneficial as these may be deleterious to the longevity of the peritoneal membrane, and in clinical trials, patients using these solutions over conventional dextrose-based solutions maintain superior preservation of RKF over time. There is no difference in membrane failure, technique failure, or patient survival shown with use of low-GDP, neutral-pH solutions over conventional PD solutions. Most notably, low-GDP solutions do not improve UF compared to traditional glucose-based solutions with suggestion of diminished UF compared to conventional glucose-based PD solutions in some studies, which has been purported by some to be the driving force for the increases in residual kidney volume seen versus the consequence of a direct biocompatible renoprotective effect of these solutions.

Amino Acid–Based Solutions

Development of amino acid-based solutions was driven to improve the nutritional status of patients by allowing for intraperitoneal amino acid absorption, which has been met with limited evidence for benefit and concerns of metabolic acidosis, limiting their long-term use. The most commonly used solution is a 1.1% amino acid (87 mmol/L) concentration and is recommended for use once daily. There is no benefit to UF with amino acid solutions, and they effectively perform similarly to the UF one would anticipate using 1.5% dextrose dialysate.

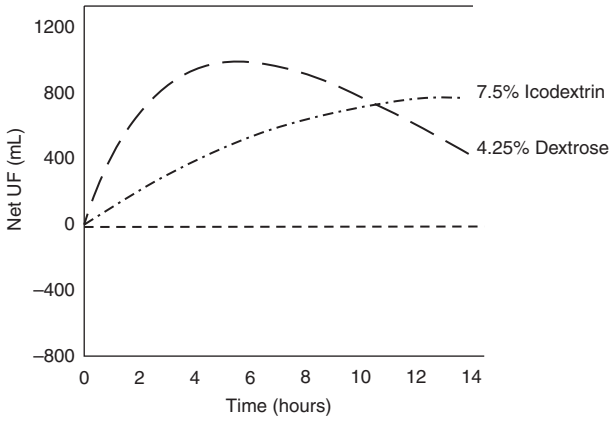
Icodextrin

Icodextrin is a mixture of glucose polymers formed from corn starch, which is minimally absorbed across the peritoneum due to its large size. While icodextrin does not cross the peritoneal membrane, it can be absorbed via lymphatics and is hydrolyzed to maltose, maltotriose, and matotetraose in the body. It is important to understand that icodextrin is not carbohydrate free, and while there is significantly less carbohydrate absorption, some still occur. Icodextrin has 250 g carbohydrate per 2 L, of which approximately 25% will be absorbed in an eight-hour dwell. Another way to describe this is with the concept of UF efficiency, which describes the amount of UF in milliliter per gram of carbohydrate absorbed. Icodextrin has greater efficiency compared to 2.5% dextrose, with UF efficiency of 27.8 mL/g of carbohydrate absorbed compared to 7.9 mL/g for dextrose-based solutions.

Icodextrin is used to increase UF in the long dwell for PD patients (day exchange in APD patients and overnight exchange in CAPD patients) because it allows for slow continuous UF. Icodextrin use in the developed world has been steadily increasing ever since its approval by regulatory bodies. There has been less uptake of use in developing countries due to the cost of icodextrin, and it is not widely available in many low-income countries. Icodextrin induces UF by colloid osmosis largely through small pores in the peritoneal membrane without the recruitment of aquaporins, which allows for exclusively sodium-coupled fluid transport. Compared to standard dextrose solutions, there is no water removal in excess of sodium, and this prevents sodium sieving (see APD section).

Multiple clinical trials have shown that icodextrin provides improved UF for the long dwell as compared with dextrose solutions (which in many cases would result in net fluid reabsorption during a similar time period if a 1.5% solution is the comparator) and results in fewer episodes of volume overload. In a Cochrane review, icodextrin was compared to dextrose solutions, and it was demonstrated that icodextrin performed superiorly with a mean difference in UF of 510.55 mL, favoring icodextrin over glucose solutions. See Fig. 24.3 for a comparison of icodextrin versus 4.25% dextrose solution and their UF profiles. Further, a systematic review and meta-analysis by Goossen et al. demonstrated probable decreased mortality with icodextrin use. Additional benefits from icodextrin are the attractive glucose-sparing properties, improvements in lipid markers, and improved echocardiographic parameters with reduction in left ventricular end-diastolic diameter and reduction in left ventricular mass.

When using icodextrin for fluid removal, one must appreciate that UF properties are dependent on dwell time, with icodextrin maximally beneficial over dextrose when used in a long dwell (typically 10–14 hours), although maximal effects may be achieved by 10 hours, with minimal further anticipated UF after this time (although no absorption). Icodextrin further has been shown to be maximally effective in people with fast PSTRs, which are arguably a group that may stand to benefit from UF enhancements. Twice-daily icodextrin has been used for enhanced UF with success but remains an off-label indication.



• **Fig. 24.3** Ultrafiltration *(UF)* with icodextrin is a slow continuous process, compared to UF with 4.25% dextrose solution, which results in a peak UF at an earlier time point. Icodextrin is useful for UF over a long period of time, but in the event of acute volume overload, a dextrose solution should be used to achieve UF more rapidly.

Optimizing Peritoneal Dialysis Prescription for Sodium and Water Removal

Peritoneal Dialysis Modality

Both CAPD and APD are effective at removing sodium and water; thus, patient preference and lifestyle should be weighed heavily when deciding on the appropriate PD modality. Cochrane review data elicit that choice of CAPD versus APD has not been shown to have significant difference with respect to mortality, risk of peritonitis, switching from original PD modality to a different dialysis modality, hernias, PD fluid leaks, PD catheter removal, RKF, or hospital admissions. Similarly, there is no difference in maintenance of euvolemia or health-related quality of life when CAPD is compared to APD. Taken all together, despite the limitations of these studies largely being observational with a paucity of RCT data, existing evidence would suggest that both modalities are effective for PD patients; while peritoneal membrane solute transfer rate status should be identified early on in PD therapy, this should not limit patients to one modality over the other as both UF and small solute clearance are similar between the two modalities. It has previously been recommended that peritoneal membrane characteristics dictate the choice of PD modality, specifically that people with fast PSTRs be assigned APD to allow for short cycles and loss of osmotic gradient, while those with slow PSTRs be assigned to CAPD to allow for extended time periods for solute and fluid transfer. However, given the body of literature, the absence of a readily available PET result at the onset of PD therapy, and typically the presence of significant RKF at the start of PD, the lifestyle and preference of

the patient should have significant bearing when deciding on modality. Peritoneal membrane function may be more relevant for people with fast PSTRs who, over time, may require APD to maintain UF (particularly as RKF declines) given the rapid dissipation of dextrose gradient, which can lead to absorption on the longer CAPD dwells. In the next sections, we will review strategies to manipulate the PD prescription in both CAPD and APD to enhance fluid removal.

Continuous Ambulatory Peritoneal Dialysis Prescription Optimization

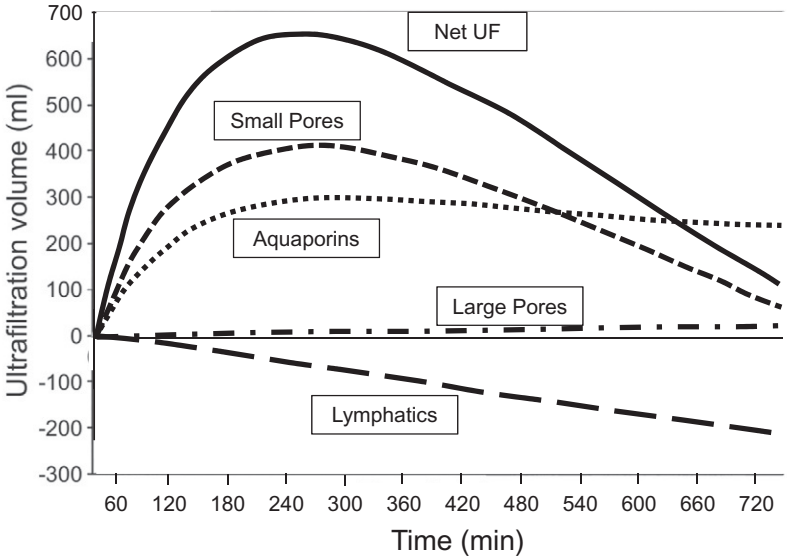
One of the benefits of CAPD is it has been purported to have superior sodium removal as compared to APD. A recent systematic review and meta-analysis by Borrelli et al. that reviewed seven cohort studies including 683 patients demonstrated that dialysate sodium removal is significantly higher in CAPD as compared to APD, while UF remains the same with both modalities. This may be driven by sodium sieving that occurs on APD (discussed in the next section), which may be hindering sodium removal in APD. However, these studies need to be interpreted with caution as the additional overfill volume of CAPD solution to accommodate a "flush-before-fill" technique (approximately 200 mL) may not have been fully accounted for in the calculation of total sodium removal in the CAPD group, leading to overestimation of sodium removal in CAPD. Standard CAPD prescriptions include four exchanges (typical dwell length four hours): three manual daytime dwells and one long overnight dwell. Typically, the number of daytime exchanges will be dictated by the UF necessary for the patient, and in incident patients with significant RKF, one may commence PD with fewer exchanges, and increase incrementally as more solute and water clearance is needed. Over time, longitudinal studies of peritoneal membrane function have demonstrated that as PSTRs increase CAPD may lead to excess salt and water accumulation. This is because of both enhanced glucose absorption and diminished peritoneal UF as a result of these peritoneal membrane changed coupled with RKF decline. Acutely, the use of higher dextrose concentrations should be considered, but excessive use of hypertonic (4.25%) solutions may be deleterious for the peritoneal membrane, and a more long-term strategy should be sought after. In this regard, shortening the dwell period by adding additional CAPD dwells and limiting dwells associated with fluid reabsorption can prevent excess salt and water accumulation. However this is limited as increasing number of dwells beyond four daytime exchanges becomes increasingly burdensome for patients, impacting overall quality of life. Another strategy is to add an icodextrin overnight dwell. Twice-daily icodextrin can also be used to facilitate UF. However, in many, transition to APD may be necessary to facilitate dwell times that are much shorter and increase UF if the diminished UF is related to increasing PSTRs. If diminished UF is due to reduced osmotic conductance to glucose (suggested by significantly reduced UF on the PET as discussed earlier), a transition to APD may not be as successful in facilitating further sodium and water removal.

Automated Peritoneal Dialysis Prescription Optimization

As mentioned earlier, one of the major differences between APD and CAPD is dialysate sodium removal; less sodium may be removed on APD due to shorter dwell times, which can result in sodium sieving. Sodium sieving occurs because water molecules can be removed independent of solute through water-specific aquaporins (ultrasmall pores) or coupled with sodium removal through small and large pores across the peritoneal membrane. Early on in the dwell, water transport by the peritoneal aquaporins is greatest, thereby creating a rapid drop in dialysate sodium concentration due to heightened free water peritoneal losses. Later in the dwell, aquaporin recruitment relaxes as a greater contribution of water removal comes from the small pore channels, which is sodium-coupled water transport (Fig. 24.4). If PD dwells are excessively short, this may lead to enhanced water-only removal via aquaporins and sodium sieving, in which reduced sodium removal may result in hypernatremia stimulating thirst and may counteract the intended goal of net fluid removal. Sodium sieving is more likely to occur with high tonicity dextrose solutions. Rodriguez-Carmona et al. demonstrated that while sodium removal was lower in APD patients compared to CAPD patients, the addition of an icodextrin long dwell, daytime manual exchanges, and lengthening the APD dwell times all resulted in significantly increased sodium removal in APD, and thus, each of these strategies provide a clinically important tool to enhance sodium removal in APD patients.

An individual's APD overall cycler time should initially be based on the amount of time the patient sleeps overnight so as to limit interference with daily routine. Based on the number of hours they sleep, the number of dwells can be set, with typical dwell times averaging 90–135 minutes. If the dwell is too short, this may promote sodium sieving and also prevent maximal peritoneal UF; this can be exacerbated if the time for filling and draining (average 30 minutes) is excessive, as can be the case in the face of mechanical disruptions, which can further limit the time available for fluid removal. To prevent this, it is recommended that no more than five exchanges in a nine-hour period for people with faster PSTRs (dwell length 108 minutes), and no more than four exchanges in those with slower PSTRs (dwell length 135 minutes). Increased cumulative time on the cycler with additional exchanges is a useful strategy to increase UF, as long as it does not interfere with patient lifestyle.

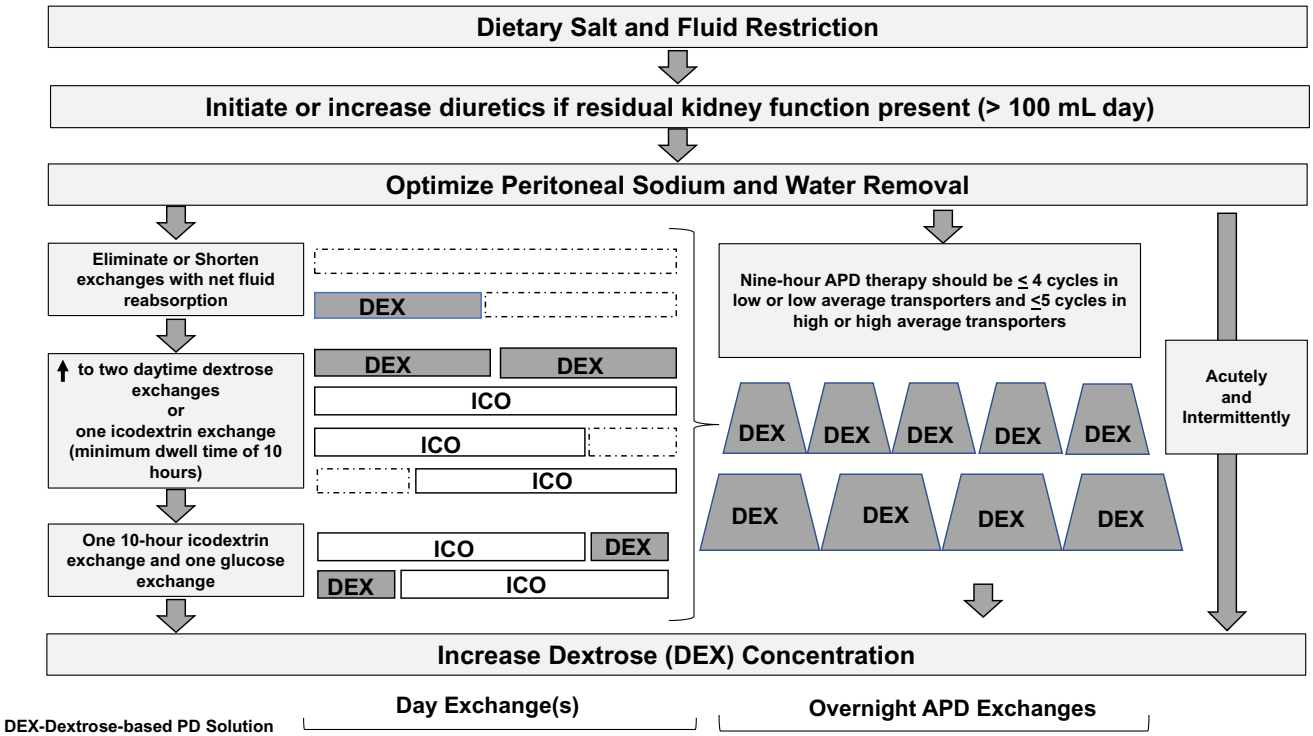
With regard to the daytime period in APD, a dextrose solution for the long dwell may be more deleterious than no dwell at all as it can lead to fluid reabsorption. If day exchanges are needed for solute clearance, dextrose can be replaced with icodextrin as it has been established that icodextrin is superior to dextrose-based solutions at achieving UF in the long dwell of APD patients. The addition of daytime exchanges has been shown to improve UF and,



• **Fig. 24.4** Contribution of Peritoneal Membrane Pores to Combined Ultrafiltration (UF) Over time. Note that early in the dwell, aquaporins contribute significantly to UF (results in sodium sieving if dwell is terminated within this time period), but their role diminishes over time as more UF is achieved through small pores. Minimal UF occurs through large pores. The lymphatic system will provide a constant low rate of fluid absorption.

in particular, sodium removal. Both lengthened time on cycler and daytime exchanges are reasonable options, and ultimately, the choice should be based on input from the patient and lifestyle considerations. These two strategies can also be combined together, which is commonly seen in anuric patients (see later). The recommended stepwise approach to fluid overload management in the APD patient can be viewed in Fig. 24.5.

For patients with acute volume overload on APD, hypertonic dialysate can be used, much like in their CAPD counterparts, but again should be used as a rescue and, if possible, minimized long-term exposure.



• **Fig. 24.5** Stepwise Approach to Management of Fluid Overload in APD Patients. There is no added benefit to UF beyond ten hours with icodextrin. *APD*, Automated peritoneal dialysis; *DEX*, dextrose; *ICO*, icodextrin. (Used with permission from Trinh E, Perl J. The patient receiving automated peritoneal dialysis with volume overload. *Clin J Am Soc Nephrol*. 2018;13(11):1732–1734.)

Causes of Impaired Peritoneal Membrane Ultrafiltration

a) *Peritoneal membrane UF failure:* True UF failure is defined as the inability of the peritoneal membrane to remove > 400 mL on a standard 4.25% PET or failure to UF > 200 mL on a 2.5% PET. However, in many cases, volume overload is the result of an imbalance between sodium and water intake and excretion (worsened by loss of RKF) in the face of a functional peritoneal membrane as evidenced by adequate UF on a PET. When true UF failure occurs, there are a few causative possibilities: neovascularization, fibrosis of the peritoneal membrane, or a combination of both. The fibrotic changes result in the loss of aquaporin function and significantly reduced osmotic conductance to glucose, while neovascularization results in increased permeability of the membrane and the loss of UF due to failure to maintain the osmotic gradient of dextrose. The latter can be addressed with shortened dwells offered by APD, but the former may not be remediable with prescription modification. Both of these processes can occur over time but may not necessarily occur simultaneously. There are some unique situations resulting in diminished UF that one should always be cognizant of, including rapid and excessive lymphatic absorption and mechanical complications, which can be mistaken for UF failure and are discussed later.

b) *Mechanical complications:* Mechanical complications including catheter malfunction, leaks, and hernias are common problems that lead to a sudden drop in UF; they should be ruled out any time there is a significant drop in peritoneal UF. Catheter malfunction most commonly is caused by fecal loading, with other causes of catheter malfunction including fibrin, wrapping of the catheter in omentum, or tip migration. Peritoneal fluid leakage into the surrounding soft tissue, genital leaks, or pleural leaks will also result in low UF, and suspicion for these processes should be raised if patients present with abdominal fullness (with no other areas of fullness), slow catheter flow rates, or localized edema/fluid collection.

c) *Excess peritoneal lymphatic absorption:* Intraperitoneal fluid absorption via the lymphatic system occurs in all PD patients and typically has an approximate volume of 80–90 mL per hour. Thus, in PD patients, net UF is the net result of transperitoneal fluid movement minus lymphatic absorption. See Fig. 24.4 for lymphatic absorption in relation to UF. In rare cases, patients have persistent reabsorption of hypertonic and non–dextrose-based fluid. This is a rare complication and often will present early in the PD therapy (not a late complication), necessitating a transition to HD. While advanced diagnostics for lymphatic absorption measurements have been developed, a clinical clue will be persistent and excessive fluid absorption even in the face of an icodextrin exchange.

Emerging and Novel Dialytic Strategies to Enhance Peritoneal Sodium and Water Removal

Bimodal Solutions

Bimodal PD solutions consist of an admixture of icodextrin and dextrose; these can be considered for those who want a glucose sparing strategy or those with inadequate UF. When bimodal solutions (2.61% glucose and 6.8% icodextrin) were compared to icodextrin alone in a small study by Freida et al. of seven prevalent PD patients with fast peritoneal transport rates, the bimodal solution produced significantly higher UF and sodium removal than icodextrin alone. Similar results with improved UF were seen in a small study by Jenkins and Wilkie, and they additionally compared bimodal solutions to 3.86% glucose alone, finding a similar UF profile between these two solutions. Both of these studies showed that the bimodal solutions were well tolerated by patients. As mentioned, bimodal solutions have increased sodium removal as compared to conventional PD solutions, particularly in the study by Freida et al., which is likely due to their lower sodium concentration in the bimodal solution (Na-121 mmol/L), allowing for diffusive losses. These solutions are attractive for glucose-sparing regimens and can be used for enhanced UF, but there is concern, particularly with the lower sodium concentration, that it may precipitate hyponatremia. These solutions are currently under investigation, and more data are needed before their routine clinical use.

Low-Sodium Dialysate

Low-sodium PD solutions can be used to correct sodium balance and thus improve volume status. Multiple different types include noncompensated solutions (Na-102 mEq/L with no increased glucose concentration), compensated solutions (Na 115 mEq/L with additional glucose to maintain osmotic pressure), and modest noncompensated solutions (Na-125 mEq/L without additional glucose). These solutions facilitate greater diffusive removal of sodium; however, the noncompensated solutions result in loss of osmotic pressure and, thus, a decline in UF and have had no impact on BP. This is in contrast to the compensated solutions, which provide diffusive sodium loss, maintain convective removal, and have BP-lowering effects; the negative impact with compensated solutions is higher glucose concentration and the metabolic concerns that arise. Modest noncompensated solutions have the ability to allow for significant sodium removal and positive BP-lowering effects with only a small reduction in UF as compared to standard solutions. These solutions are experimental and are currently not routinely used due to a paucity of data but may become more relevant in the future of PD for patients with significant sodium retention, particularly given their ability to increase sodium removal.

Acute Volume Overload Management

Patients presenting with acute volume overload can often be managed with PD and do not require a transition to HD. In those with RKF, higher doses of diuretics should be used in addition to increasing UF on PD. Management in this setting is aimed at rapid removal of fluid, and in this case, it is reasonable to use hypertonic dextrose solution with more rapid exchanges to achieve rapid fluid removal. Icodextrin should not be used for acute volume overload as it is a slower form of fluid removal that is less effective than dextrose over a short period of time (see Fig. 24.3). Patients should undergo frequent exchanges every 3–4 hours continuously to achieve a negative balance. This can be done with continuous manual exchanges or extension of cumulative time on APD with increased number of cycles, which theoretically can be employed for 24 hours per day. A key element to success in volume overload is targeting the osmotic equilibrium for UF with a specific solution and doing very short dwells (for example, exchange every hour) in this case will be detrimental to fluid removal goals. For example, with a 4.25% solution, osmotic equilibrium time for UF is approximately 4 hours (see Fig. 24.2A), and shorter cycles will result in submaximal UF. It is important to monitor for hypokalemia in this setting as it is a common complication with frequent exchanges.

Fluid Removal in the Anuric Patient

In anuric patients, it becomes that much more critical to know how to manipulate the PD prescription to enhance sodium and water removal both acutely and for the long-term prescription. Once a PD patient has become anuric, they can remain on PD safely, as demonstrated in the European APD Outcomes Study (EAPOS). The EAPOS is a prospective, observational, multicenter study that followed 177 APD patients over a 2-year period; patients at study outset were predominantly anuric or had urine volume less than 100 mL/day. The study showed 78% patient survival at 2 years and 62% technique survival; age, diabetes, protein-energy wasting (assessed by subjective global assessment), and baseline peritoneal UF of less than 750 mL per day were associated with a higher risk of death. UF was not time dependent in this study, and an association with mortality was only seen for baseline UF, not changes or rates of decline of UF over time. The importance of peritoneal UF was again highlighted in a study by Lin et al. that retrospectively reviewed a cohort of anuric PD patients in China and found that a UF greater than 1 L was associated with greater patient and technique survival compared to those with a UF less than 1 L. It is important to remember that these are observational studies and thus do not dictate a threshold or target UF in anuric PD patients. Given the observational nature of the study, patients with higher UF may have had general better nutrition status necessitating extra UF as opposed to a specifically protective effect from the UF itself. Strict adherence to fluid and sodium restrictions becomes paramount to prevent hypervolemia in anuric patients, and clinicians need to routinely be vigilant for signs of UF failure due to reduced osmotic conductance to glucose, increased PSTRs, or both. It is not uncommon for anuric patients to require regular use of 2.5% or even 4.25% dextrose solutions. A standard maximal APD prescription would include 9–10 hours on the cycler (with four to six exchanges) plus a last fill with icodextrin and up to one–two additional day time manual exchanges. Jeloka et al., in a prospective study of 36 PD patients in Canada and Turkey, demonstrated that no further UF with icodextrin was achieved after the 10-hour dwell point. As such, in APD patients, the last fill of icodextrin can be drained at 10 hours to facilitate additional daytime manual exchange before or after the icodextrin dwell to enhance volume removal (see Fig. 24.5 for manipulations to APD prescription in volume overload). For CAPD, a standard maximum prescription would include four manual exchanges during the day with a long overnight dwell of icodextrin. For CAPD patients on maximal PD with ongoing volume overload, a transition to APD may be considered. In an APD patient on a maximal prescription, it may reach a point where PD becomes too burdensome on the patient and further intensification of PD to achieve fluid targets makes PD no longer attractive. In this case, transition planning should be considered an alternate kidney replacement therapy modality.

Conclusion

Volume overload is a common and complex problem faced by many patients on PD, requiring a multidisciplinary approach to successfully manage. Controversies still exist in the tools and methods by which ideal volume status is evaluated and established among patients. Currently, a combination of multiple physical exam features plus investigations with BIA and US can be used to establish volume status in patients. Left ventricular mass remains a controversial target for volume management strategies for patients receiving PD and may be a cause or a consequence of chronic volume overload. Identification of the underlying cause for fluid overload can guide in the appropriate management strategies. Both failure to UF and UF failure can occur, and it is important to delineate between these, given that the former may be remediable with dialytic and nondialytic strategies. The tools in this chapter provide a stepwise approach to the treatment options that can be considered to enhance sodium and water removal in patients receiving PD. Ultimately, when discussing these treatment options, the impact that these changes may have on patient lifestyle and patient-reported outcomes is a penultimate consideration. In many cases, while further dialytic enhancements to peritoneal sodium and water removal may be possible, this must be balanced against the burden of the therapy, and quality of life as perceived by the patient and appropriate transition

to an alternate therapy may need to be considered. Using shared decision making, it is always important to evaluate whether patient treatment goals are being achieved with PD, and in many cases, optimal volume management may form a critical component of these discussions.

Recommended Reading

ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension.* 2017;71(4):e13-e115.

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Peritoneal Access Devices, Placement Techniques, and Maintenance

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The success of peritoneal dialysis (PD) as kidney replacement therapy for end-stage kidney disease and acute kidney injury relies upon a functional access to the peritoneal space for exchange of water and solutes. This access represents a controlled cutaneoperitoneal fistula comprised of a catheter device that bridges the abdominal wall through which fluid exchanges occur. Knowledge of best practices in catheter placement and maintenance can optimize the success of therapy and minimize the risk of catheter complications. To serve as a practical resource for the management of adult kidney failure patients, this chapter will focus on current practices, describing the most commonly used catheter types, procedures for matching the most appropriate device to the patient, placement methods, break-in procedures, and catheter care and maintenance. Investigational PD devices and techniques are not discussed. Pediatric dialysis access is covered in Chapter 70.

Selection of catheter devices and insertion techniques often varies depending on whether the access is needed for acute or long-term PD therapy, geographic availability of material resources, and local provider expertise in placing catheters.

Acute Catheters

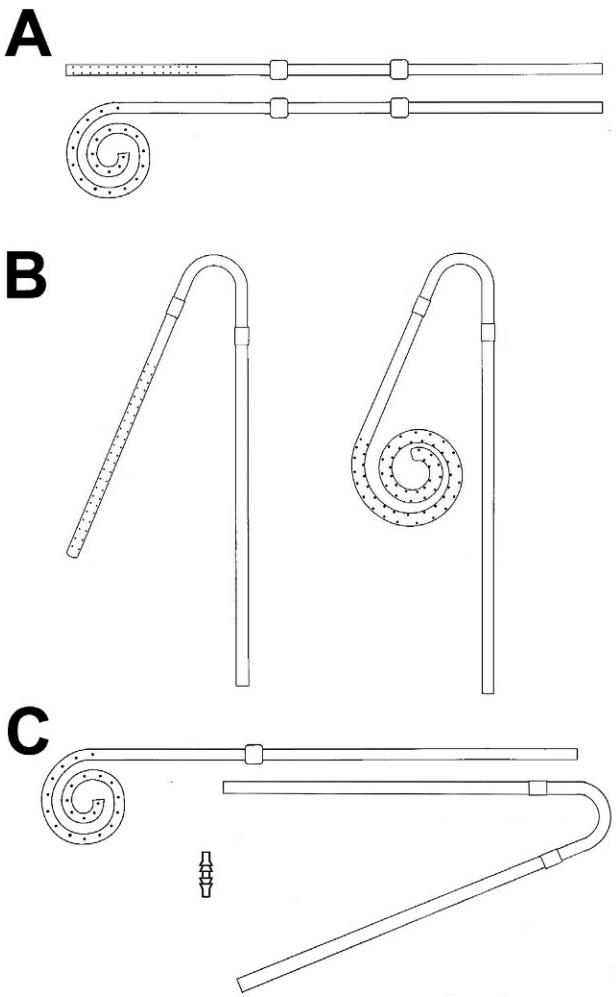
Flexible silicone rubber cuffed catheters for long-term PD (described more fully in the following section) are also routinely utilized for acute peritoneal access. Temporary semirigid plastic noncuffed catheters continue to be used for acute kidney injury in some lower-resource countries. The rigid acute catheter is inserted by percutaneous puncture using an internal stylet. The small lumen and side holes tend to be associated with less efficient dialysis. Pericatheter leakage and tubing obstruction are common. Because the risk of infection is high with rigid noncuffed catheters, the generally accepted period of maximum use is 3 days.

Silicone rubber catheters have supplanted the rigid device for acute access because they have a larger-diameter lumen and side holes, resulting in better dialysate flow rates and less obstruction. They are less prone to leakage and have a lower incidence of peritonitis. If the patient does not recover kidney function, the catheter may be used for long-term dialysis without the need for a new access procedure.

Chronic Catheters

The majority of catheters for long-term use are constructed of silicone rubber. The most commonly employed PD catheter types are illustrated in Fig. 25.1. The standard double Dacron (polyester) cuff and straight- and coiled-tip catheters with a straight or preformed arc bend in the intercuff segment constitute the mainstay of PD access around the world (Fig. 25.1A and B). A recent large randomized controlled study comparing straight- and coiled-tip catheter configurations implanted by open dissection significantly favored the straight-tip design; however, the incidence of flow dysfunction was very low for both groups. A critical review of this study noted that the results were not adjusted for midline muscle-sweeping vs. paramedian muscle-splitting catheter insertion sites or operator/facility locations of the procedure. Previous smaller randomized trials comparing straight- and coiled-tip catheters have produced conflicting results with regard to the superiority of one design over the other.

Even though standard catheters are available with single cuffs, there is evidence to support the superiority of double-cuff catheters in preventing peritonitis from periluminal entry of organisms. A large retrospective cohort study suggested that the effect of the number of cuffs on peritonitis may be era related. Patients initiating PD from 1996 to 2000 had a significantly lower peritonitis rate with double-cuff catheters than with single-cuff devices, attributed mostly to lower rates of *Staphylococcus aureus.* In a later interval, 2001–2005, no difference in peritonitis rates was observed based upon the number of cuffs. The widespread adoption of prophylactic exit site or intranasal antibiotics during the later period may have reduced exit site colonization and infection sufficiently to eliminate the



• **Fig. 25.1** Commonly Used Peritoneal Catheters. (A) Catheters with a straight intercuff segment, two cuffs, and straight or coiled tips. (B) Catheter with a preformed intercuff arc bend, two cuffs, and straight or coiled tips. (C) Extended catheter with one cuff, coiled-tip abdominal catheter, two-cuff extension catheter with preformed intercuff arc bend, and titanium double-barbed connector. (Crabtree JH, Shrestha BM, Chow KM, et al. Creating and maintaining optimal peritoneal dialysis access in the adult patient: 2019 update. *Perit Dial Int*. 2019; 39:414–436, Figure 1.)

need for protection by the second cuff. However, the benefit of a double cuff may be particularly important where prophylactic antibiotics are not used. Since patient adherence with prophylactic ointments is variable, having the added protection of a double cuff may be advantageous, especially among those with diabetes and immunosuppressed patients in whom the risk of *S. aureus* catheter infection is higher.

Most catheters for long-term use possess a white radiopaque stripe along the longitudinal axis of the tubing that permits radiographic visualization. The stripe also serves as a guide during catheter insertion to prevent accidental twisting or kinking of the tubing. The majority of adult catheters have a 2.6-mm internal diameter. One catheter brand possesses a 3.5-mm internal diameter and can be readily identified by its blue radiopaque stripe. Although the in vitro flow rate of the larger-bore catheter is faster, any therapeutic advantage of this device has yet to be proven in the in vivo state. The importance of recognizing the catheter bore size is to prevent interchange of repair kits and replacement catheter adapters that can result in a loose fit and accidental separation.

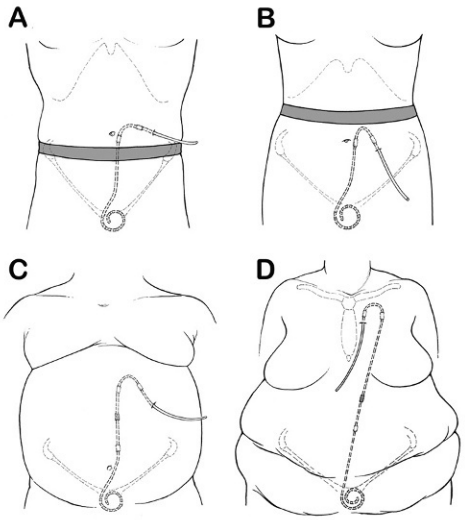
Extended two-piece catheters were originally designed to provide a presternal exit site (see Fig. 25.1C). The extended catheter consists of a one-cuff abdominal catheter segment that attaches to a two-cuff subcutaneous extension segment using a double-barbed titanium connector to permit remote location of the exit site to the upper chest. Extended catheters are also used to provide remote exit site locations to the upper abdominal and back regions. The abdominal catheter can be placed by any insertion method. The subcutaneous extension catheter is implanted using a vascular tunneling rod or similar device supplied by the catheter manufacturer.

Various modifications of the basic catheter designs have been made in an attempt to address the common mechanical problems of tissue attachment, tip migration, and pericatheter leaks. However, none of these alternative configurations have been shown to outperform the catheter designs depicted in Fig. 25.1 but increase the cost and difficulty of device insertion and removal. Concerns for these common mechanical problems are more reliably addressed by proper implantation technique than by a catheter design.

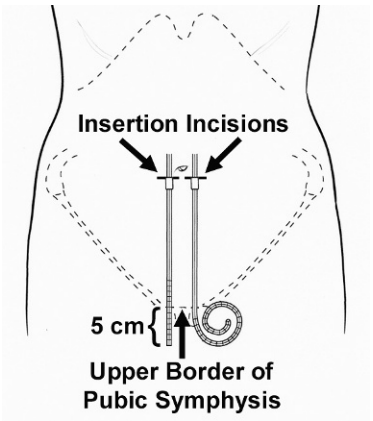
Choosing a Peritoneal Catheter for Long-Term Use

Because patients come in all sizes and shapes with a variety of medical conditions, it is unrealistic to expect that one catheter type should fit all. The choice of catheter type should take into consideration the patient's belt line, obesity, skin creases and folds, presence of scars, chronic skin conditions, incontinence, physical limitations, bathing habits, and occupation. The provider's familiarity with a basic inventory of catheter types is essential to enable customization of the peritoneal access to the specific needs of the patient and to afford maximum flexibility in exit site location. An exit site located in an area susceptible to mechanical irritation, bacterial contamination, or in a position that the patient cannot easily see or take care of predisposes to exit site and tunnel infection.

Fig. 25.2 illustrates how a basic catheter inventory might be applied. Patients who wear their belt lines below the umbilicus or have lower abdominal skin folds are usually best fitted with a catheter having a straight intercuff segment that is bent to produce a laterally directed exit site emerging above the belt line. Patients who wear their belt lines above the umbilicus are often best served with a catheter with a preformed arc bend that allows the exit site to emerge below the belt line. Individuals who have large rotund abdomens, severe obesity, drooping skin folds, intestinal stomas, feeding tubes, suprapubic catheters, urinary or fecal incontinence, chronic yeast intertrigo, or desire to take deep tub baths are candidates for extended two-piece catheters to produce upper abdominal or presternal exit sites.



• **Fig. 25.2** Practical Applications of a Basic Catheter Inventory. (A) Straight intercuff segment catheter with laterally directed exit site emerging above a low-lying belt line. (B) Preformed intercuff arc bend catheter with downwardly directed exit site emerging below a high-lying belt line. (C) Extended catheter with an upper abdominal exit site for an obese rotund abdomen, lower abdominal skin folds, or incontinence. (D) Extended catheter with presternal exit site for severe obesity, multiple abdominal skin folds, intestinal stomas, or incontinence. (Crabtree JH, Chow KM. Peritoneal dialysis catheter insertion. *Semin Nephrol*. 2017; 37:17–29, Figure 3.)



• **Fig. 25.3** Schematic of a supine patient showing the method in which the catheter insertion site and deep cuff location are determined in order to achieve optimal pelvic position of the catheter tip. For straight-tip catheters, ideally, a design with 15 cm of tubing length beyond the deep cuff, a point 5 cm from the tip of the catheter is aligned with the pubic symphysis upper border. With coiled-tip catheters, the upper border of the coil is aligned with the upper border of the pubic symphysis. (Crabtree JH, Shrestha BM, Chow KM, et al. Creating and maintaining optimal peritoneal dialysis access in the adult patient: 2019 update. *Perit Dial Int*. 2019; 39:414–436, Figure 3.)

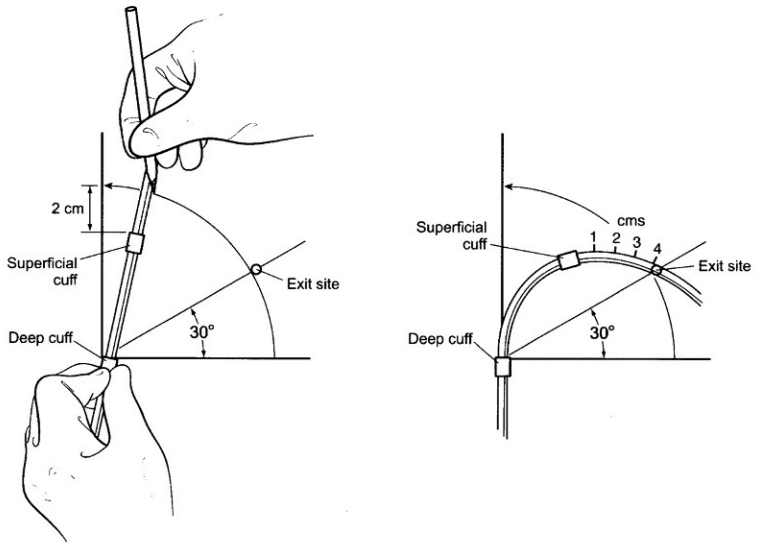
The most appropriate choice of catheter is the one that produces the best balance of pelvic location of the catheter tip, exit site easily visible to the patient, and can be inserted through the abdominal wall with the least amount of tubing stress. The catheter insertion site is the fulcrum of this best balance and will determine the pelvic position of the catheter tip and the range of reachable exit sites. Therefore, catheter selection begins with determination of the insertion site. With the patient in the supine position, the insertion site for each style and size of catheter is determined by marking the upper border of the deep cuff in the paramedian plane when the upper border of the catheter coil is aligned with the upper border of the pubic symphysis (Fig. 25.3). For straight-tip catheters, a point 5 cm from the end is aligned with the upper border of the pubic symphysis. During the catheter placement procedure, the deep cuff is implanted within the rectus muscle (or just below) at the level of the insertion incision. Using this convention to determine the insertion site will prevent the catheter tip from being implanted too low in the pelvis, producing pressure or poking discomfort, early termination of dialysate outflow, and severe end of drain pain.

After determining the catheter insertion site, the subcutaneous tunnel path and exit site location for catheters with a swan-neck bend simply follows the arc-bend configuration of the tubing, marking the skin exit site 2–3 cm beyond the superficial cuff. Catheters with a straight intercuff segment should assume a gentle arc in the subcutaneous tissues to produce more of a laterally directed exit site. Illustrated in Fig. 25.4 is a convenient three-step algorithm for catheters with a straight intercuff segment to design a laterally directed tunnel and exit site that minimizes creation of excessive tubing stress and shape-memory resiliency forces that can lead to catheter tip migration and superficial cuff extrusion. The amount of subcutaneous tube straightening over time is a balance between the induced catheter shape memory resiliency forces and the resistance offered by the tissues. In the worst-case scenario of tube straightening, the algorithm prevents the superficial cuff from coming closer than 2 cm of the exit site. In actual practice, the cuff remains 3 to 4 cm from the exit site. Even though this configuration is referred to as a laterally directed exit site, note that the terminal end of the subcutaneous track is inclined slightly downward to prevent pooling of water and debris in the skin exit sinus.

If the catheter needs to be arced more than a laterally directed exit site, a swan-neck catheter should be used instead to eliminate induced resiliency forces. Upwardly directed exit sites should be avoided to prevent pooling of cutaneous bacteria and debris, perspiration, and shower water in the exit sinus, predisposing the patient to exit site and tunnel infection.

After mapping exit site locations, the patient assumes a sitting or standing position and the marked exit sites are checked to see which is best visualized by the patient and does not conflict with the belt line, skin creases, or apices of bulging skin folds. If none of the marked exit sites for the standard abdominal catheters are satisfactory, the patient is then considered for an extended catheter to produce an upper abdominal or presternal exit site location.

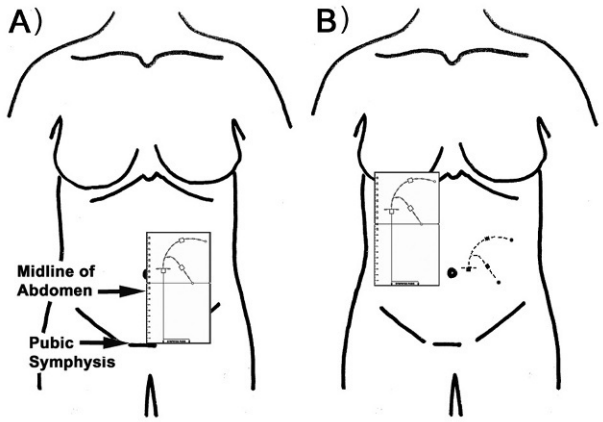
Some dialysis catheter manufacturers produce marking stencils for the most commonly used coiled-tip catheter designs. Properly constructed stencils contain critical catheter design information including the distance between the deep



• **Fig. 25.4** Three-Step Algorithm for Lateral Tunnel Track and Exit Site Design. Step 1: scribe arc from the vertical to the horizontal plane using catheter as compass from point 2 cm external of superficial cuff. Step 2: mark exit site at junction of medial two-thirds and lateral one-third of the arc. Step 3: indicate tunnel track shape by bending the catheter over from point 4 cm external of the superficial cuff to the exit site. (Crabtree JH. Selected best demonstrated practices in peritoneal dialysis access. *Kidney Int*. 2006;70:S27–S37, Figure 10.)

cuff and the coil, suggested subcutaneous tunnel configurations, and recommended exit site locations relative to the position of the superficial cuff. Additional features of a well-designed stencil plate permit its precise orientation on the trunk region according to fixed anatomical landmarks, such as the pubic symphysis, representing the anterior upper border of the true pelvis, and the anatomical midline of the torso. Stencils permit accurate and reproducible association of the catheter design elements to these anatomical landmarks to help determine the best catheter type and insertion site that will produce optimal pelvic position of the catheter coil and the exit site location, which is reachable from the determined catheter insertion site. An example of a marking stencil and its use to map two types of standard abdominal catheters is illustrated in Fig. 25.5. Most commercially available stencils use the three-step algorithm depicted in Fig. 25.4 to indicate the suggested lateral configuration of the subcutaneous track of straight intercuff segment catheters. The subcutaneous tunnel track for swan neck catheters follows the precise shape of the preformed arc bend. It is important to note that because of variations in dimensions of catheters among manufacturers, stencils cannot be used interchangeably for different product lines.

The advantages offered by stencil-based preoperative mapping is that the patient can be fully informed of the catheter insertion procedure, including the device type and exit site location and to assure that the facility has acquired the selected catheter type for the day of the procedure. In addition to the preoperative evaluation, the marking stencil is used again at the time of the catheter placement procedure to retrace the previously determined insertion incision, tunnel configuration, and exit site location. Be aware that some manufacturers produce impractical stencils that show only the cutout patterns of a swan neck bend but do not allow for proper alignment of the stencil plate on the abdominal or chest wall.



• **Fig. 25.5** Stencil-Based Preoperative Mapping. (A) Marking stencil is aligned on the abdominal wall to determine the insertion site for the straight intercuff segment and swan neck catheters that produces optimal pelvic position of the catheter tip and indicates exit sites that can be reasonably reached from this point using the most favorable tunnel configurations. (B) Straight intercuff segment and swan neck catheters are mapped on the abdominal wall.

Peritoneal Dialysis Catheter Placement Procedures

Independent of the catheter implantation approach, adherence to a number of universal details is required to

ensure the best opportunity for creating a successful long-term peritoneal access. Best practices for preoperative preparation and peritoneal catheter placement are listed in Table 25.1. Omission of any one of these practices can potentially lead to loss of the catheter. Some implantation techniques do not incorporate all of the best practices, such as percutaneous needle-guidewire approaches performed through the midline or positioning the deep cuff above the level of the fascia. It is essential that the practitioner be aware of deviations from recommended practices and be observant for the potential complications that may arise from such departures.

PD catheters are ordinarily placed by open surgical dissection, percutaneous needle-guidewire with or without image guidance, and laparoscopy. Table 25.2 provides suggested guidelines for selecting a catheter implantation approach. A brief summary of each of these techniques follows.

Open Surgical Dissection

A transverse or vertical paramedian incision is made through the skin, subcutaneous tissues, and anterior rectus sheath. The underlying muscle fibers are split to expose the posterior rectus sheath. A small hole is made through the posterior sheath and peritoneum to enter the peritoneal cavity. A purse-string suture is placed around the opening. The catheter, usually straightened over an internal stylet, is advanced through the peritoneal incision toward the pelvis. Despite being an open procedure, the catheter is advanced mostly by feel, therefore, blindly, into the peritoneal cavity. The stylet is partially withdrawn as the catheter is advanced until the deep cuff abuts the posterior fascia. After satisfactory placement has been achieved, the stylet is completely withdrawn and the purse-string suture is tied. Encouraging the catheter tip to remain oriented toward the pelvis is achieved by oblique passage of the catheter through the rectus sheath

TABLE 25.1 Best Practices in Peritoneal Catheter Placement

Patient Preparation

- Preoperative assessment to select the most appropriate catheter type, insertion site, and exit site location.
- Implement a bowel program to prevent perioperative constipation.
- Shower on the day of procedure with chlorhexidine soap wash of the planned surgical site.
- If hair removal is necessary, use electric clippers.
- Empty the bladder before the procedure; otherwise, a Foley catheter should be inserted.
- Single preoperative dose of prophylactic antibiotic to provide antistaphylococcal coverage.

Procedure Performance

- Operative personnel are attired in cap, mask, sterile gown, and gloves.
- The surgical site is prepped with chlorhexidine-gluconate scrub, povidone-iodine (gel or scrub), or other suitable antiseptic agent and sterile drapes applied around the surgical field.
- Peritoneal catheter is rinsed and flushed with saline and air squeezed out of the Dacron cuffs by rolling the submerged cuffs between fingers.
- Paramedian insertion of the catheter through the body of the rectus muscle.
- Deep catheter cuff positioned within or below the rectus muscle.
- Pelvic location of the catheter tip.
- Place purse-string suture(s) around the catheter at the level of the peritoneum and posterior rectus sheath and/or the anterior rectus sheath.
- Catheter flow test performed to confirm acceptable function.
- Subcutaneous tunneling instrument should not exceed the diameter of the catheter.
- Skin exit site directed lateral or downward (not upward).
- Exit site located ≥2 cm beyond superficial cuff.
- Exit site should be the smallest skin hole possible that allows passage of the catheter.
- No catheter anchoring sutures at the exit site (use medical liquid adhesive and sterile adhesive strips to secure the catheter).
- Attach the dialysis unit's requested catheter adapter and transfer set at time of procedure.
- Exit site protected and catheter immobilized by nonocclusive dressing.

TABLE 25.2 Suggested Guidelines for Selecting a Peritoneal Dialysis Catheter Insertion Approach

	Previous Major Surgery or Peritonitis (Order of Suggested Technique)	No Previous Major Surgery or Peritonitis (Order of Suggested Technique)
Patient suitable for general anesthesia	• Advanced laparoscopic • Open surgical dissection	• Advanced laparoscopic • Image-guided percutaneous • Open surgical dissection • Percutaneous without image guidance
Patient only suitable for local anesthesia	• Open surgical dissection	• Image-guided percutaneous • Open surgical dissection • Percutaneous without image-guidance

Modified from Crabtree JH, Shrestha BM, Chow KM, et al. Creating and maintaining optimal peritoneal dialysis access in the adult patient: 2019 update. *Perit Dial Int*. 2019;39:414–436, Table 2.

in a craniocaudal direction. The catheter tubing is exited through the anterior rectus sheath at least 2.5 cm cranial to the level of the purse-string suture and deep cuff location. Attention to detail in placement of the purse-string suture and repair of the anterior fascia is imperative to prevent pericatheter leak and hernia. The catheter is tunneled subcutaneously to the selected exit site following a satisfactory test of flow function.

Percutaneous Needle-Guidewire Technique

Placement of catheters by blind percutaneous puncture is performed using a modification of the Seldinger technique. The convenience of this approach is that it can be performed at the bedside, under local anesthesia, and using prepackaged self-contained kits that include the dialysis catheter. The abdomen is prefilled with 1.5–2 L of saline or dialysis solution instilled with an 18-gauge introducer needle inserted through a 1.5–2 cm infraumbilical or paramedian incision. Alternatively, a Veress needle may be used to perform the prefill. A guidewire is passed through the needle into the peritoneal cavity and directed toward the pelvis. The needle is withdrawn. A dilator with an overlying peel-away sheath is advanced through the fascia over the guidewire. The dilator is removed. The PD catheter is advanced through the peel-away sheath over the guidewire. Alternatively, the guidewire is removed from the peel-away sheath and the PD catheter, straightened over an internal stylet, is advanced through the sheath. The stylet is partially withdrawn as the catheter is advanced. The dialysis catheter is directed toward the pelvis. As the deep catheter cuff advances, the sheath is peeled away. The deep cuff is advanced to the level of the fascia. The peel-away sheath and guidewire or internal stylet, if used, are removed. Ideally, the deep cuff should be pushed through the fascia into the rectus muscle and a purse-string suture placed around the catheter to minimize the risk of pericatheter leak.

The addition of image guidance using ultrasonography and fluoroscopy increases the reliability and safety of the percutaneous approach. Ultrasound can be used to visualize the passage of the needle into the peritoneal cavity and avoid the inferior epigastric vessels and bowel loops. Fluoroscopy permits confirmation of needle entry into the peritoneal cavity by observing the flow of injected contrast solution around loops of bowel. The retrovesical space is identified by contrast pooling in the appropriate location. The guidewire and catheter are advanced to this site. The remainder of the procedure proceeds as described for blind placement. Although the radiopaque tubing stripe permits fluoroscopic imaging of the final catheter configuration, the proximity of adhesions or omentum cannot be assessed. After testing flow function, the catheter is then tunneled subcutaneously to the selected exit site.

Laparoscopy

Laparoscopy provides a minimally invasive approach with complete visualization of the peritoneal cavity during the catheter implantation procedure. The advantage of laparoscopic catheter placement over other approaches is the ability to proactively employ adjunctive procedures that significantly improve catheter outcomes. Laparoscopically guided rectus sheath tunneling places the catheter in a long musculofascial tunnel directed toward the pelvis and effectively prevents catheter tip migration, eliminates pericatheter hernias, and reduces the risk of pericatheter leaks. Observed redundant omentum that lies in juxtaposition of the catheter tip can be displaced from the pelvis into the upper abdomen and fixed to the abdominal wall (omentopexy). Compartmentalizing adhesions that may affect completeness of dialysate drainage can be divided. Intraperitoneal structures that siphon up to the catheter tip during the intraoperative irrigation test can be laparoscopically resected, including epiploic appendices of the sigmoid colon, uterine tubes, and the vermiform appendix. Redundant and bulky rectosigmoid colon blocking the pelvic inlet can be suspended along the lateral abdominal wall

(colopexy). Previously unsuspected abdominal wall hernias can be identified and repaired at the time of the catheter implantation procedure.

Through a lateral abdominal wall puncture site remote from the point of intended catheter insertion, the abdomen is insufflated with gas through a Veress needle to create an intraperitoneal working space. A laparoscopic port and laparoscope are inserted. Under laparoscopic guidance, the catheter is introduced at a second puncture site and placed in a musculofascial tunnel oriented toward the pelvis, usually through the use of a port device that creates the rectus sheath tunnel. The catheter tip is directed into the true pelvis under visual control. After removal of the port device used to insert the catheter, the deep cuff of the catheter is positioned in the rectus muscle just below the anterior rectus sheath entry point. A purse-string fascial suture is placed around the catheter at the level of the anterior sheath to minimize the risk of pericatheter leak. The pneumoperitoneum is released but laparoscopic ports are left in place until a test irrigation of the catheter demonstrates successful flow function. After any indicated adjunctive procedures are completed, the catheter is tunneled subcutaneously to the selected exit site.

Testing Hydraulic Function

It is important to test catheter flow function before ending the catheter placement procedure. If the catheter has poor hydraulic function, catheter position should be adjusted until satisfactory flow is achieved. There are no standard protocols for hydraulic testing. A simple test is to inject 60 mL of saline into the catheter. Easy return of some of this fluid and changes in the level of an air–fluid interface in the tubing during respiration confirm that the catheter is located in the peritoneal space and has no kinks. A more complete test of flow function consists of infusing 500 to 1000 mL of saline or dialysate and observing for unimpeded inflow and outflow, allowing a 100- to 200-mL residual volume to remain to avoid leaving peritoneal structures drawn up to the catheter side holes. The larger irrigation volumes may permit an opportunity for redundant omentum, epiploic appendices, uterine tubes, or vermiform appendix to siphon up to the catheter tip and cause slow or low volume drainage. Adjusting the position of the catheter may possibly correct the flow dysfunction. Advanced laparoscopic techniques can definitively identify and deal with the anatomical structures impairing the flow and reduce the risk for future mechanical complications. The larger irrigation volume also provides an assessment of hemostasis and washes out any collection of blood from the procedure.

Special Peritoneal Access Methods

Extended Two-Piece Catheters

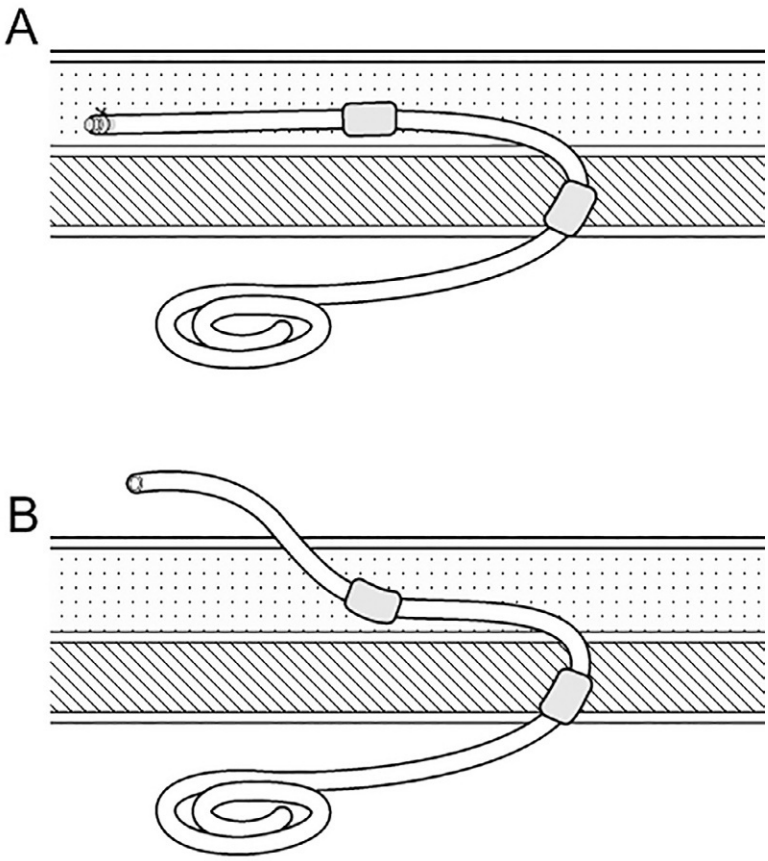
The abdominal segment of two-piece extended catheters can be implanted by any of the above-mentioned insertion techniques. A secondary incision is made in the vicinity of the planned upper abdominal, presternal, or back exit site. A marking stencil is invaluable in devising the location of the secondary incision and exit site. The measured distance between the abdominal insertion incision and the secondary incision is used to calculate how much tubing length will be trimmed from one or both of the catheter segments in order to correctly span the distance. The trimmed catheters are joined with a double barbed titanium connector and the linked catheter segments are tunneled on the surface of the fascia from the abdominal insertion site to the remote secondary incision with a tunneling rod. The extension catheter is then passed from the secondary incision through a subcutaneous tunnel to the designated exit site using a stylet to complete the procedure.

Catheter Embedding

Commonly referred to as the Moncrief-Popovich technique, catheter embedding consists of implanting a PD catheter far in advance of anticipated need. Instead of bringing the external limb of the catheter out to the surface, it is embedded under the skin in the subcutaneous space. When kidney function declines to the point of needing to initiate dialysis, the external limb is brought to the outside through a small skin incision (Fig. 25.6).

After externalization of an embedded catheter that has been afforded extended healing time within the abdominal wall, the patient is able to proceed directly to full volume PD without the necessity of a break-in period that ordinarily accompanies a newly placed catheter. Another important attribute of catheter embedding is greater patient acceptance for earlier commitment to PD by catheter placement ahead of time. Once an embedded catheter is in place, patients tend to remain faithful to their modality selection. Consequently, this technique can be used as a strategy to grow PD programs. The need for insertion of central venous catheters and temporary hemodialysis can be avoided in patients previously implanted with an embedded catheter. The embedding technique permits more efficient surgical scheduling of catheter implantation as an elective nonurgent procedure and helps to reduce stress on operating room access. Disadvantages of the catheter embedding strategy include the need for two procedures (implantation and externalization) as opposed to one and the possibility of futile placement in the event of an adverse change in the patient's condition during the time period that the catheter is embedded.

Catheter embedding can be incorporated into any of the implantation approaches using any catheter device. The catheter is temporarily externalized through the future skin exit site prior to embedment. The exit site scar serves as a landmark to know where to come back to for externalization. After acceptable flow function of the catheter is confirmed, the tubing is flushed with heparin, plugged, and buried in the subcutaneous tissue. To minimize the risk of hematoma or seroma and to facilitate subsequent externalization, the catheter should be embedded in a linear or curvilinear subcutaneous track using a tunneling stylet as



• **Fig. 25.6** The Embedded Catheter Strategy. (A) The external limb of the catheter tubing is embedded under the skin at the time of catheter placement. (B) The external limb of the catheter is externalized when renal function declines to the point that dialysis is required.

opposed to curling the tubing into a subcutaneous pocket. Embedding should not be performed if the anticipated need for dialysis is less than 4 weeks. Externalization of embedded catheters is easily performed as an office procedure. Catheters have been embedded for months to years with an 85% to 93% immediate function rate upon externalization. Catheter dysfunction is usually due to intraluminal fibrin clots or adhesions. Overall, 94% to 99% are successfully used for dialysis after radiologic or laparoscopic revision of nonfunctioning catheters.

Acute Complications of Peritoneal Dialysis Catheter Placement

Inadvertent preperitoneal position of the introducer needle, peel-away sheath, and catheter can occur during acute or long-term peritoneal catheter placement using percutaneous stylet or needle-guidewire approaches. Inflow of dialysate will be slow and painful and the outflow minimal with the effluent often becoming blood-tinged. If preperitoneal placement is suspected, drain as much fluid as possible, remove the catheter, and repeat the insertion process.

In addition to preperitoneal catheter placement, blood-tinged outflow can represent injury to a blood vessel in the abdominal wall or mesentery. The return will usually clear with continued dialysis. Grossly bloody effluent, fall in hematocrit, or signs of hemodynamic instability signify large blood vessel injury. Urgent laparotomy is generally required. Unexplained polyuria and glycosuria suggest accidental puncture of the urinary bladder. If the needle has entered the bowel, instillation of dialysate will be accompanied by pain and/or an urgent need to defecate. Unrecognized bowel entry may be heralded by feces or gas in the effluent or watery diarrhea having a high glucose content. Surgical intervention is often necessary. If surgical exploration is planned, it is beneficial to leave the catheter in place so that the site of perforation can be more easily identified.

Catheter Placement Approaches and Best Outcomes

It is often argued that no single catheter placement approach has been shown to produce superior outcomes. Operator performance aside, when catheter implantation by open surgical dissection, percutaneous needle-guidewire with or without image guidance, and laparoscopy are compared side to side on identical study populations with equivalent adherence to best practices, the results are essentially equal. It should be of no surprise that if laparoscopy is used only to witness the position of the catheter tip, the outcomes are no

TABLE 25.3 Best Practices Specific for Laparoscopic Peritoneal Catheter Placement

- No midline abdominal entry points for laparoscopic ports
- Immobilize catheter toward the pelvis by rectus sheath tunneling or lower abdominal suture sling (no pelvic anchoring stitches)
- Omentopexy performed for redundant omentum when it is noted to rest within the juxtaposition of the catheter tip
- Adhesiolysis performed to enable catheter placement and/or to eliminate recognized intraperitoneal compartmentalization that can impede dialysate drainage
- Laparoscopic port wound is not used as a catheter skin exit site
- Irrigation test completed before removal of laparoscopic ports in case additional interventions required
- Suture closure of all laparoscopic port sites regardless of port size if acute or urgent dialysis is anticipated

Crabtree JH, Shrestha BM, Chow KM, et al. Creating and maintaining optimal peritoneal dialysis access in the adult patient: 2019 update. *Perit Dial Int*. 2019;39:414–436, Table 25-3.

different than any other catheter insertion method. Simply using the laparoscope to locate the catheter is underutilization of this modality and should be viewed as substandard practice. The advantages of laparoscopy over every other technique are the adjunctive procedures enabled by this method, principally rectus sheath tunneling, omentopexy, and adhesiolysis. When these techniques are applied effectively, the advanced laparoscopic approach can both prevent and resolve most of the common mechanical problems that complicate insertion of PD catheters. To ensure optimal outcomes, Table 25.3 includes additional best practices that are specific for laparoscopy.

Care of the Long-Term Peritoneal Catheter

Postoperative Catheter Immobilization and Dressings

Since no catheter skin anchoring stitches should ever be used, it is important to immobilize the catheter on the abdominal wall with medical adhesive tincture and sterile adhesive strips. A nonocclusive barrier dressing of sufficient size to protect the exit site and surgical wounds and to further immobilize the catheter should be applied at the time of the placement procedure. In addition, the transfer set should be secured to the abdominal wall to prevent tugging on the catheter at the exit site. It is helpful to secure the transfer set to the abdominal wall separately from the main dressing so that the PD nurses have access to the tubing for catheter irrigations without having to disturb the dressing over the exit site. As long as the dressings are clean and intact and the exit site appears stable, dressings are changed on a weekly basis until such time that the patient is instructed in the protocol for long-term exit site care. If at any time the exit site appears unstable, the frequency of exit site care is modified according to the findings.

Catheter Irrigation

Catheters that are not used immediately should undergo irrigation with 1 L of solution (saline or dialysate) within 72 hours following insertion to wash out blood and fibrinous debris. If the effluent is particularly bloody, irrigation is repeated until signs of clearing are evident. To ensure patency, it is a good idea to repeat the irrigation weekly until such time that dialysis is instituted. Heparin added to the irrigant (1000 units/L) is helpful in preventing fibrin plugging of the catheter during the early postoperative period.

Catheter Break-in Procedures

Nonurgent Start

When feasible, delaying start of dialysis for 2 weeks following catheter insertion helps to reduce the risk of pericatheter leakage. Either continuous ambulatory PD or automated PD can be initiated after this period. Although most patients can begin dialysis with 2 L volumes, starting with lower volumes and increasing incrementally to target levels can be performed during the training period.

Urgent Start

PD catheters can be used immediately postimplantation if care is taken to create a tight seal at the insertion site. Although no standard dialysis prescription exists for patients starting urgent PD, a low-volume, supine, intermittent PD protocol is advisable to minimize the risk of leak. Such an approach might consist of initiating automated exchanges using 1–1.25 L volumes and increasing the amount by 250–500 mL per week. The abdomen should be left dry during ambulatory periods for the first 2 weeks.

Long-Term Catheter and Exit Site Care

Patients should limit themselves to nonstrenuous activities for 4–6 weeks following catheter placement to permit good wound healing. If exit site healing is uneventful, most patients are able to resume showering in 3–4 weeks. This usually coincides with implementation of the chronic exit site care routine. Most exit site care protocols involve daily cleansing with nonirritating, nontoxic, antiseptic agents and application of a prophylactic antibiotic ointment or cream such as mupirocin or gentamicin. Sterile dressings over the exit site are encouraged. Tub bathing and swimming with immersion of the exit site are discouraged. Centers that permit swimming usually restrict the activity to properly chlorinated private pools or ocean water. It is recommended that an ostomy appliance or similar device cover the exit

site and catheter during swimming and to perform routine exit site care after the activity. Patients should be reminded that the catheter is a "lifeline" and advised to consider the consequences of risking exposure of their peritoneal access to potential contamination during swimming.

Embedded Catheter Care

Patients who undergo catheter embedment may resume showering after 48 hours. Nonstrenuous activities are required for 4–6 weeks following catheter placement to permit good wound healing. Externalization of embedded catheters is a clinic procedure performed using sterile technique in a suitable treatment room under local anesthesia. If appropriate embedding technique was performed, the catheter tubing should be easily palpable at the incision scar created during the procedure while the catheter was temporarily externalized at the future exit site. In equivocal cases, ultrasound examination has been employed to identify the catheter tubing at the correct distance from the superficial cuff. Care is exercised in anesthetizing the skin and making the incision to avoid damage to the catheter. Hemostat dissection is used to identify and deliver the catheter from the embedment track. The plugged end of the tubing is amputated, catheter adapter inserted, transfer set attached, and flow function tested. The catheter may require brisk irrigation with a 60 mL syringe and saline to dislodge fibrin clots. Unsatisfactory flow function should be managed as described under the section on mechanical complications and management. Exit site care following externalization of embedded catheters is the same as described for primarily externalized catheters.

Complications of Peritoneal Catheters for Long-Term Peritoneal Dialysis

Mechanical and infectious complications are the two most common reasons for PD failure. With early and appropriate intervention, many catheters can be saved, often without interruption of therapy, or, in the event of catheter loss, the interval before return to PD can be minimized.

Mechanical Complications and Management

Mechanical complications of the catheter include pericatheter leaks and hernias, infusion and drain pain, flow failure, catheter tip migration, and superficial cuff extrusion.

Pericatheter Leaks and Hernias

Leakage around the catheter is usually related to catheter implantation technique, timing of initiation of dialysis, initial dialysate volumes, and strength of abdominal wall tissues. When dialysis is initiated, subcutaneous leakage may occur at the catheter insertion site and usually manifests itself as fluid appearing through the incision or at the exit site. Questionable leaks can be verified by a positive glucose dipstick indicating high glucose concentration in the leaking fluid. Delaying initiation of dialysis for 2 weeks following catheter placement minimizes the risk for developing a leak. Temporarily discontinuing dialysis for 1–3 weeks usually results in spontaneous cessation of an early leak. Dramatic early leaks may indicate purse-string suture failure or technical error in wound repair and requires immediate exploration. Leakage through the exit site or insertion incision leaves the patient susceptible to tunnel infection and peritonitis. Prophylactic antibiotic therapy should be employed. Persistent leaks necessitate catheter replacement.

Late pericatheter leaks are caused by pericannular hernia or occult tunnel infections with separation of the cuffs from the surrounding tissues. The occurrence of pericannular hernia is largely influenced by the location and degree of fixation of the deep cuff. At the parietal peritoneal surface, the mesothelium reflects along the surface of the catheter to reach the deep cuff. If the deep cuff was placed outside of the muscle wall or the cuff shifts outward because of weak midline fascial attachments, then the peritoneal lining actually extends above the fascial layer creating the potential for a subcutaneous sac filled with dialysate. This fluid-filled subcutaneous mass is referred to as a pseudohernia and can eventually lead to a pericatheter leak. If the abdominal wall is weak, a pericannular track may dilate and develop a true hernia. Most late leaks and pericatheter hernias are best managed by catheter replacement.

Infusion and Drain Pain

Pain during dialysate infusion is ordinarily observed in new patients initiating dialysis and is often transient in nature, gradually disappearing over several weeks. Persistent infusion pain is commonly associated with the acidity (pH 5.2–5.5) of conventional lactate buffered dialysis solutions. Use of bicarbonate/lactate-buffered dialysis solutions (pH 7.0–7.4) can eliminate this pain. If buffered solutions are not available, manual addition of bicarbonate to each dialysis bag (4–5 meq/L) can be performed to treat acid-related infusion pain. Alternatively, a 1% or 2% lidocaine solution added to the dialysate (5 mL/L) may be tried to lessen infusion discomfort.

Other causes of dialysate-related pain include hypertonic glucose solutions, aged dialysis solution, overdistention of the abdomen, or extremes in dialysate temperature. Catheter malposition with the tip against the abdominal wall or tube restriction by attached tissues can produce both inflow and outflow pain. Slower infusion rates and incomplete drainage may diminish these symptoms; however, transluminal catheter manipulation or laparoscopic exploration should be considered for flow pain that is persistent or accompanied with flow dysfunction with or without associated catheter malposition.

Pain during outflow is common, especially toward the end of the drain phase, particularly in the early period after initiation of dialysis. As the intraperitoneal structures siphon up to the catheter tip during the drain, it causes the catheter to bump up against the exquisitely sensitive

parietal peritoneum. The pain is frequently experienced in the genital or anorectal region. Drain pain is more often a problem with automated PD due to hydraulic suction on the peritoneal lining. Catheters implanted too low on the abdominal wall can wedge tubing into the deep pelvis, resulting in drain pain from early closure of pelvic viscera around the catheter tip. Similarly, constipation with crowding of the bowel around the catheter in the pelvis can cause or contribute to the severity of the symptoms. The drain pain sometimes resolves with time or with treatment of associated constipation. If persistent, it can be managed by avoiding complete drainage of the peritoneal effluent. In cycler patients, this can be achieved by performing tidal PD. On occasion, conversion of automated PD patients to continuous ambulatory PD has helped with severe drain pain by eliminating cycler hydraulic suction. In resistant cases of drain pain, catheter replacement is indicated with the tip positioned higher in the pelvis.

Flow Failure

Catheter flow dysfunction ordinarily manifests as outflow failure where the volume of drained dialysate is substantially less than the inflow volume and there is no evidence of leakage around the catheter or through other peritoneal boundary defects. Outflow failure usually occurs soon after catheter placement, but it may also begin during or after an episode of peritonitis, or at any time during the life of the catheter.

The most common cause of outflow dysfunction is constipation. Distended rectosigmoid colon may block the catheter side holes or displace the catheter tip into a position of poor drainage function. Extrinsic bladder compression on the catheter due to urinary retention occurs less frequently. An abdominal radiograph is helpful to look for a fecal-filled colon and catheter displacement. Constipation is treated with oral administration of osmotic laxatives, such as lactulose or polyethylene glycol solution. Stimulant laxatives such as bisacodyl and saline enemas are reserved for refractory cases since chemical and mechanical irritation of the colonic mucosa has been associated with transmural migration of bacteria and development of peritonitis.

Mechanical kinking of the catheter tubing is usually accompanied by two-way obstruction. A flat-plate or lateral radiograph of the abdomen is often helpful in identifying a kink in the catheter tubing. Catheter revision or replacement will be required.

Another cause of two-way obstruction is fibrin plugging of the catheter. Heparin should be added to the dialysate whenever fibrin strands are visible in the effluent. Heparin is more useful prophylactically than therapeutically, preventing the formation of fibrin clots and propagation of existing clots. Once outflow obstruction has occurred, dwelling the catheter with heparin is frequently unsuccessful in recovering function. If flow function is not restored with heparin, thrombolytic therapy with tissue plasminogen activator (tPA) may be attempted. Failure to dislodge intraluminal debris by brisk irrigation of the catheter with saline is followed by instillation of tPA. If catheter obstruction is due to a fibrin clot, recovery of flow function with tPA has been reported at nearly 100%. Because of cost considerations, the dose of tPA (used in dilution of 1 mg/mL) is based upon the estimated volume of the catheter assembly; however, no adverse consequences have been documented for catheter overfill or repeat administration.

If treatment of constipation and fibrinolytic therapy are not successful in restoring drainage function and urinary retention, and tubing kinks have been excluded, the catheter is presumed to be obstructed by omentum or other adherent intraperitoneal structures. Interventions to resolve catheter obstruction, most commonly utilize radiologic and laparoscopic techniques.

Radiologic intervention by fluoroscopic guidewire manipulation has been used to redirect displaced and obstructed catheters. Stiff guidewire manipulation of catheters with a swan neck bend can be difficult to perform and painful to the patient. Forcible straightening of the subcutaneous tunnel can produce tissue trauma and infection. Transluminal manipulation is not possible for extended catheters because of the long tubing length. A preprocedure dose of prophylactic antibiotics to provide antistaphylococcal coverage is advisable. Particular attention must be given to antiseptic preparation of the catheter tubing in addition to creating a sterile surgical field for the procedure. The transfer set is disconnected and discarded. After catheter manipulation is performed, restoration of flow function is checked by syringe irrigation. Frequently, multiple, separate manipulation procedures are required with long-term flow function restored in only 45%–73% of cases. Failure rates for fluoroscopic manipulation as high as 90% were observed when patients had an antecedent history of abdominopelvic surgery or peritonitis, suggesting that adhesions play a major factor in technical failures.

Laparoscopy has become an invaluable method of evaluating and resolving catheter flow obstruction. Because laparoscopy can reliably identify the source of flow dysfunction and provide a means for definitive treatment, it is often considered as the next step in the management sequence after other causes for obstruction have been excluded. The dialysis catheter frequently can be used to perform the initial gas insufflation of the abdomen since most catheter obstructions represent outflow problems. Alternatively, a Veress needle is used for insufflation or the initial laparoscopic port is an optical trocar device or a port placed by direct cut-down on the peritoneum. Laparoscopic exploration is performed to identify the source of obstruction. Additional laparoscopic ports for the introduction of operating instruments may be required depending on the findings.

Omental attachment to the catheter coil, with displacement of the tubing out of the pelvis, is a common cause of cause of outflow dysfunction. Omental entrapment is relieved by using laparoscopic grasping forceps to strip the omentum from the catheter. The catheter tip is temporarily exteriorized through one of the port sites to facilitate removal of residual intraluminal tissue debris. The omentum

is laparoscopically sutured to the upper abdominal region (omentopexy) to keep it away from the catheter. Redundant epiploic appendices of the sigmoid colon and uterine fimbria may siphon up to the catheter coil and produce obstruction. Laparoscopic resection of the involved epiploic appendices and uterine tube prevents recurrent obstruction. Obstruction of the catheter by adhesive scar tissues can be treated by laparoscopically dividing the adhesions or simply pulling the catheter free of the adhesions if they are not too extensive. Adhesiolysis for poor drainage function, especially after peritonitis, is associated with a 30% failure rate secondary to reforming of adhesions.

Catheter Tip Migration

Migration of the catheter tip to a position of poor drainage function is frequently caused by shape-memory resiliency forces of a straight catheter bent into a configuration that imposes excessive stress on the tubing. Simply repositioning the catheter will be followed by recurrence of the migration in a high percentage of cases. Laparoscopic suturing of the catheter tip to a pelvic structure has an unacceptable rate of failure due to erosion of the suture. A more reliable approach is to laparoscopically place a suture sling in the suprapubic region through the abdominal wall and around the catheter. A sling will maintain the catheter toward the pelvis and not hinder catheter removal if required at a later date.

Superficial Cuff Extrusion

Erosion of the superficial cuff through the exit site can result from positioning the cuff too close (< 2 cm) to the exit wound during catheter placement. In addition, excessive bending of the catheter with a straight intercuff segment to produce a downward exit direction can induce mechanical stresses on the tubing. In combination with close proximity of the cuff to the exit site, the shape-memory forces of a catheter bent into this configuration can lead to tube straightening over time with migration of the superficial cuff toward and through the exit site. Another cause for superficial cuff erosion that can eventually result in extrusion of the entire catheter is outer displacement of the tubing due to poor location and fixation of the deep cuff. Also, exit site infection extending to the superficial cuff may cause it to separate from the surrounding tissues and extrude through the exit site.

An extruded cuff becomes a reservoir of bacteria within the vicinity of the exit wound. Aggravated by daily wetting of the cuff material during routine exit site care, the presence of the infected cuff interferes with maintaining exit site hygiene. Using a scalpel blade applied parallel to the cuff surface, the cuff is shaved in repetitive slices until all of the cuff material is removed. The blade should be changed frequently to ensure ease in performing the shave without applying undue pressure that could risk cutting into the lumen of the tubing. If the cuff material cannot be safely removed, simultaneous catheter replacement, described later in the section on PD-related peritonitis, may be an alternative management strategy if the exit site remains unstable.

Surgical Management of Catheter-Related Infections

Details on antibiotic treatment for catheter infections are discussed in Chapter 26. The eventual outcome of a chronic exit site infection with superficial cuff involvement is a tunnel abscess or progression of the tunnel infection to the peritoneal cavity producing concurrent peritonitis. Early recognition of chronic exit site and tunnel infection is essential to providing the best opportunity for catheter salvage.

Exit Site and Tunnel Infection

Exit site infection presents as redness, swelling, and tenderness at the exit site. With tunnel involvement, the signs of infection extend along the subcutaneous course of the catheter. In most cases, exit site and tunnel infections are accompanied by purulent discharge from the exit site. In chronic smoldering cases, the exit site skin is loose around the catheter, granulation tissue is present at the skin exit sinus, and purulent material can be expressed through the exit orifice with pressure over the subcutaneous cuff or stroking the skin over the tunnel toward the exit site while gently tugging on the catheter. As long as the infection has not extended to the deep cuff, it is possible to resolve the problem without losing the catheter or interrupting therapy. Ultrasonography of the catheter tunnel is a useful preoperative tool to evaluate for deep cuff involvement, particularly in obese patients where physical signs are often unreliable. Patients found to have sonographic evidence of deep cuff infection should undergo catheter removal. Moreover, patients with concurrent peritonitis are not candidates for catheter salvage procedures, this condition suggesting that transmural spread of the infection has already occurred.

If the deep cuff is not involved, surgically opening up the subcutaneous tunnel and shaving the superficial cuff is an option. Unroofing the skin and subcutaneous tissue overlying the infected tunnel permits drainage of pus, debridement of granulation tissue, and removal of the cuff material. The catheter, including the shaved tubing segment, is directed out of the medial corner of the incision and stabilized in this position by securing it to the adjacent skin with medical adhesive tincture and sterile adhesive strips. The wound is left open with the performance of once- or twice-daily wet to dry dressing changes with saline-soaked gauze and allowed to heal by secondary intention. Depending upon the magnitude of the infection, the procedure can be performed in the treatment room or operating room under local or general anesthesia. The primary advantage of the unroofing-cuff shaving procedure is that dialysis is not interrupted.

An alternative surgical treatment approach for chronic exit site infection that has not extended beyond the superficial cuff into the intercuff section is replacement of the infected external tubing segment by catheter splicing. This may be the preferred salvage procedure for a badly chosen exit site

location that was placed in an infection-prone area, such as within a skin crease, on the apex of a flabby skin fold, or under the belt line. In this circumstance, performing only an unroofing-cuff shaving procedure may still result in an exit site location that is predisposed to infection. The spliced catheter segment can be routed to a more stable exit site location, including the upper abdomen or chest region. Since the procedure requires more extensive dissection and tunneling, it is best performed in the operating room under local or general anesthesia. Ultrasonographic examination of the subcutaneous tunnel is essential to exclude fluid in the intercuff segment, the presence of which would contraindicate a splicing procedure.

After skin preparation, the infected exit site is isolated from the primary surgical field during draping and managed in the final step to prevent contamination of the new catheter and wound. An incision is made through the previous insertion site scar to expose the uninvolved intercuff segment of the catheter at the level of the fascia. The catheter is divided in the intercuff segment to preserve a 2.5-cm stump on the deep cuff side. A single or double cuff catheter with or without a preformed swan neck bend may be selected for the splicing segment. After trimming the new catheter to appropriate length, the segment is joined to the stump of the deep cuff end of the former catheter with a double-barbed titanium connector. The external segment of the spliced catheter is tunneled to a suitable exit location remote from the infected exit site. The wound is closed and dressings applied. In the final step, the external part of the old catheter is removed, and the wound is debrided and packed open with saline wet-to-dry dressings. Antibiotics are continued for 2 to 4 weeks until the infected wound is healed. PD is continued uninterrupted.

Simultaneous catheter replacement, discussed under PD-related peritonitis, is another management strategy for chronic exit site and tunnel infection.

Catheter Infection–Related Peritonitis

The progression of an exit site and tunnel infection to the deep cuff can lead to concurrent peritonitis. Rarely, peritonitis can lead to chronic deep cuff infection and proceed in a retrograde fashion to manifest initially as a tunnel infection. Ultrasonography can be helpful in evaluating deep cuff involvement. Catheter infection–related peritonitis is best managed by catheter removal. Antibiotic treatment for peritonitis is covered in Chapter 27. Reinsertion of the dialysis catheter can be performed as early as 2 to 3 weeks following catheter removal if resolution of peritoneal symptoms is complete.

Peritoneal Dialysis -Related Peritonitis

Diagnosis and antibiotic therapy for PD-related peritonitis are covered in Chapter 27. Importantly, there must be a low threshold for removal of the PD catheter for peritonitis that is not responding appropriately to treatment. The goal is to preserve peritoneal membrane function. Peritonitis can cause peritoneal adhesions that may result in catheter obstruction, limit the dialyzable space, or produce loculations that cause incomplete dialysate drainage. Fibrosis of the peritoneal membrane may affect its capacity for ultrafiltration and transfer of solutes.

Most patients with PD-related peritonitis will show considerable clinical improvement within 48 hours of initiating appropriate antibiotic therapy. Occasionally, symptoms may persist beyond 48 to 96 hours. If patients have not shown definitive clinical improvement by 96 hours, catheter removal should be performed. In patients with pseudomonas peritonitis, catheter removal should be performed by 48 to 72 hours if there has been no clinical improvement. Immediate catheter removal is indicated for fungal peritonitis. Antimicrobial therapy should be continued for at least 2 weeks after catheter removal for refractory peritonitis. Reinsertion of the dialysis catheter can be performed as early as 2 to 3 weeks following catheter removal if resolution of peritoneal symptoms is complete, although some would recommend waiting longer for fungal peritonitis.

Often, an opportunity presents for simultaneous catheter replacement without interruption of PD for selected cases of PD-related peritonitis and exit site–tunnel infection. When appropriately applied, the procedure spares the patient from a central venous catheter, a shift to hemodialysis, the ordeal of a change in dialysis modality, and a second surgery to insert a new PD catheter. General guidelines for simultaneous catheter replacement are outlined in Table 25.4.

TABLE 25.4 General Guidelines for Simultaneous Catheter Replacement Without Interruption of Peritoneal Dialysis

- Procedure acceptable for peritonitis not due to mycobacteria, fungi, enteric organisms, or *Pseudomonas* species.
- Procedure acceptable for bacterial exit site and tunnel infections.
- Clinical signs of peritonitis must be resolved and peritoneal leukocyte count is < 100/μL.
- Continue appropriate antibiotic coverage perioperatively.
- Insert a new catheter (clean step) before removal of the old catheter (dirty step).
- Close watertight all penetrating points through the musculofascial layers of the abdominal wall.
- Utilize intermittent regimen of supine, low-volume peritoneal dialysis during interval of postoperative recovery; leave the peritoneum dry during ambulatory periods.

Crabtree JH, Siddiqi, RA. Simultaneous catheter replacement for infectious and mechanical complications without interruption of peritoneal dialysis. *Perit Dial Int.* 2016; 36:182–187, Table 25-3.

Removal of Long-Term Peritoneal Dialysis Catheters

Since firm tissue ingrowth of the Dacron cuffs has occurred by 2 to 3 weeks, long-term catheters in place for a longer period will usually require removal by surgical dissection in the operating room or suitable procedure room, especially if the deep cuff was positioned in the rectus muscle. Fascial defects will require suture repair to prevent an abdominal wall hernia.

Secondary Embedding of Long-Term Catheters

On occasion, catheter removal is performed because patients regain sufficient kidney function to discontinue dialysis, but recovery is not expected to be permanent. An alternative to removing the catheter is secondary embedding. The inconvenience and cost of catheter maintenance can be eliminated for the interim by secondary embedding while still preserving a readily available peritoneal access that can be immediately employed to its fullest extent without the complications of new catheter placement, e.g., flow dysfunction and pericatheter leak.

The procedure is performed similar to catheter splicing except that the spliced external segment is embedded. After skin preparation, the existing exit site and catheter are isolated from the primary surgical field during draping and managed in the final step to prevent contamination of the spliced catheter and wounds. An incision is made through the previous insertion site scar to expose the intercuff segment of the catheter. The catheter is divided in the intercuff segment to preserve at least a 2.5-cm stump on the deep cuff side. A single- or double-cuff catheter with or without a preformed swan neck bend may be selected for the splicing segment. After trimming the new catheter to appropriate length, the segment is joined to the stump of the deep cuff end of the former catheter with a double barbed titanium connector. The external segment of the spliced catheter is temporarily externalized at the new exit site and then tunneled into a subcutaneous bed as described in the section on embedded catheters. After the wounds are closed and protected, the remaining external segment of the former catheter is removed and the old exit site wound is excised and closed.

Recommended Reading

Chow KM, Wong SSM, Ng JKC, et al. Straight versus coiled peritoneal dialysis catheters: a randomized controlled trial. *Am J Kidney Dis.* 2020;75:39–44.

This large randomized controlled trial comparing straight- and coiled-tip catheter configurations demonstrated a significantly lower incidence of flow dysfunction with the straight-tip design.

Crabtree JH. Rescue and salvage procedures for mechanical and infectious complications of peritoneal dialysis. *Int J Artif Organs.* 2006;29:67–84.

This is a comprehensive review of mechanical and infectious complications of PD and their management.

Crabtree JH, Burchette RJ. Effective use of laparoscopy for long-term peritoneal dialysis access. *Am J Surg.* 2009;198:135–141.

A large case series analysis employing advanced laparoscopic techniques is presented demonstrating the effectiveness of adjunctive procedures (rectus sheath tunneling, omentopexy, adhesiolysis) in achieving exceptional catheter outcomes in a challenging patient population.

Crabtree JH, Burchette RJ. Peritoneal dialysis catheter embedment: surgical considerations, expectations, and complications. *Am J Surg.* 2013;206:464–471.

In this case series analysis, a step-by-step description of embedding technique for a variety of catheter types is presented along with clinical outcomes and management of complications.

Crabtree JH, Shrestha BM, Chow KM, et al. Creating and maintaining optimal peritoneal dialysis access in the adult patient: 2019 update. *Perit Dial Int.* 2019;39:414–436.

The International Society for Peritoneal Dialysis presents a comprehensive evidence-based treatise of best practices for creating and maintaining peritoneal dialysis access.

Crabtree JH, Siddiqi RA. Simultaneous catheter replacement for infectious and mechanical complications without interruption of peritoneal dialysis. *Perit Dial Int.* 2016;36:182–187.

Guidelines supported by clinical data are offered for simultaneous catheter replacement without interruption of peritoneal dialysis.

Nessim SJ, Bargman JM, Jassal SV. Relationship between double-cuff versus single-cuff peritoneal dialysis catheters and risk of peritonitis. *Nephrol Dial Transplant.* 2010;25:2310–2314.

This article represents the largest analysis to date comparing single- and double-cuffed catheters with regard to the risk for catheter infection–related peritonitis.

Shahbazi N, McCormick BB. Peritoneal dialysis catheter insertion strategies and maintenance of catheter function. *Semin Nephrol.* 2011;31:138–151.

This article nicely reviews the interaction of catheter types, insertion techniques, and operator performance as well as methodologies to maintain catheter function.

Szeto CC, Li PK, Johnson DW, Bernardini J, et al. ISPD catheter-related infection recommendations: 2017 update. *Perit Dial Int.* 2017;37:141–154.

This International Society for Peritoneal Dialysis guidelines article provides comprehensive recommendations for the management of catheter-related infections.

Voss D, Hawkins S, Poole G, et al. Radiological versus surgical implantation of first catheter for peritoneal dialysis: a randomized non-inferiority trial. *Nephrol Dial Transplant.* 2012;27:4196–4204.

This randomized controlled study compared percutaneous catheter insertion using fluoroscopic guidance versus basic laparoscopic methods (no adjunctive procedures), showing that radiological placement was a noninferior, cost-effective alternative to laparoscopic insertion.

26

Peritoneal Catheter Exit Site and Tunnel Infections

SHARON J. NESSIM, MD, MSc

Introduction

Peritoneal dialysis (PD)–related infections, including peritonitis, exit site infections, and tunnel infections, remain an important cause of morbidity and technique failure. While peritonitis is usually the most frequent and morbid event among the infectious complications, exit site and tunnel infections are relevant and concerning complications of PD. This chapter will focus on the risk factors for their occurrence, as well as optimal strategies for their prevention and management.

Definitions

Catheter-related infection is used as the collective term to describe both exit site and tunnel infections. The definition of an exit site infection has evolved over time, and there have been several classifications created to try to improve the consistency in the diagnosis and reporting of exit site infections. In the simplest terms, based on the International Society for Peritoneal Dialysis (ISPD) guidelines, an exit site infection is defined as the presence of purulent discharge, with or without erythema of the skin at the catheter–epidermal interface. While erythema is often present during an exit site infection, the presence of erythema alone in the absence of purulent drainage may reflect inflammation of the skin rather than infection. Furthermore, a positive culture from an exit site in the absence of purulent drainage should be interpreted with caution, as this may simply reflect colonization of the skin.

The PD catheter tunnel is the soft tissue space that the catheter passes through between the exit site and the peritoneal cavity. A tunnel infection is defined as the presence of clinical inflammation (tenderness, edema, induration, or erythema) over the PD catheter tunnel or by the presence of a fluid collection along the catheter tunnel on ultrasound. Since a tunnel infection usually results from migration of organisms from an infected exit site into the adjacent tunnel tract, most tunnel infections occur in the presence of an associated exit site infection with the same organism.

Frequency

Data on the frequency of exit site and tunnel infections are not as readily available as those for peritonitis. In addition to the paucity of reported data on the frequency of their occurrence, studies suggest a wide variation in the rates of catheter-related infections. Some of this variability may relate to differences in the patient populations being studied, but part of it also likely relates to the relative subjectivity in diagnosing an exit site or tunnel infection as compared with a peritonitis episode. Based on one large American observational data set of patients on PD between 1998 and 2004, 21% of patients developed an exit site infection, with an annual rate of 0.184 infections per patient-year at risk (or one infection every 65.2 patient months at risk). A similar exit site infection rate was reported in a randomized trial of exit site care among 203 Canadian PD patients (0.19 episodes per patient-year) compared to another randomized trial of 371 PD patients from Australia and New Zealand in which the exit site infection rate was 0.35 episodes per patient-year.

Causative Organisms

Several large observational databases have informed our understanding of the spectrum of organisms causing exit site infection. Approximately three-quarters of exit site infections are caused by Gram-positive organisms, with the remainder mostly accounted for by Gram-negative organisms. Among the Gram-positive bacteria, the most common organism is *Staphylococcus aureus*, which is known to colonize the nares and skin of some PD patients. Other Gram-positive organisms that can cause exit site infection include coagulase-negative *Staphylococcus*, *Corynebacterium*, and *Streptococcus* species. Among the Gram-negative organisms, the most

common cause of exit site infection by far is *Pseudomonas* species. Fungal exit site infection is usually rare but may occur with greater frequency when broad-spectrum topical antibacterial agents are used at the exit site. Since most tunnel infections occur in association with an exit site infection, the causative organisms for tunnel infection mirror those for exit site infection.

Risk Factors

Since *S. aureus* is an important and frequent cause of exit site infection, one of the major risk factors is colonization with *S. aureus*. Nasal carriage of *S. aureus* has been reported to be present in approximately half of PD patients overall, with an almost twofold higher frequency of nasal carriage among patients with diabetes. Since *S. aureus* nasal carriage can be intermittent, repeating nasal swabs over time is prudent to ensure the identification of patients who are colonized. It has been shown that *S. aureus* nasal carriage is associated with a dramatic increase in the risk of *S. aureus* exit site infection and peritonitis and that strategies to eradicate *S. aureus* nasal colonization can significantly reduce the incidence of *S. aureus* exit site infection.

In addition, factors pertaining to catheter position and orientation could augment the risk of exit site and tunnel infection. The location of the exit site is critically important to minimize the risk of exit site infection. For example, an exit site that is located under the pannus of an obese patient may lead to poor visualization of the exit site by the patient and a lower likelihood of the area remaining dry and clean. Similarly, having an exit site in close proximity to a colostomy or ileostomy may increase the risk of exit site infection. Furthermore, it is important to ensure that the exit site is not located at the level of the patient's belt line, as this could contribute to chronic irritation and subsequent infection. Another important consideration is the direction of the catheter as it emerges from the skin. Based on observational data, a downward-directed tunnel has been associated with a lower risk of infection, presumably by minimizing the risk of debris and organisms getting into the exit site. Laterally directed tunnels may similarly have a lower risk of infection.

Treatment and Outcomes

If a patient is diagnosed with an exit site infection, a Gram stain and culture of the discharge from the exit site should be obtained. Depending on the severity of the infection, the introduction of antibiotics can be deferred until the results of the Gram stain and/or culture are available, or one may elect to initiate empiric antibiotics pending the results. If the latter strategy is adopted, the initial choice of antibiotics should cover *S. aureus*, and consideration should be given to covering *Pseudomonas* as well as in patients with a history of *Pseudomonas* infections. Once the causative organism is known, the antibiotics should be adjusted accordingly. Oral antibiotics are recommended as the preferred route of administration, as topical antibiotics may be insufficient to overcome the bacterial burden of an exit site infection. There is no evidence to suggest superiority of intraperitoneal administration over oral administration for exit site infections. The optimal duration of therapy is unknown, but the ISPD recommends continuation of antibiotics until the exit site appears normal, with a minimum treatment time of 2 weeks and a more lengthy course for *S. aureus* and *Pseudomonas* infections. It is recommended that the exit site be cleansed at least daily in the presence of an exit site infection.

Since tunnel infections typically represent the extension of an exit site infection into the PD catheter tunnel tract, a longer duration of therapy of at least 3 weeks may be required when treating tunnel infection, and consideration may be given to using intraperitoneal antibiotics. Tunnel sonography can be a useful adjunct for both diagnostic purposes as well as for identifying responses to therapy.

Should an exit site or tunnel infection not resolve despite appropriate antibiotic therapy, or should a patient develop peritonitis with the same organism as that causing the catheter infection, the PD catheter should be removed. Such severe or nonresolving exit site and tunnel infections are most typical of *S. aureus* and *Pseudomonas*, which are very difficult to eradicate. For example, in one study, it was shown that complete resolution of a concomitant *Pseudomonas* exit site infection and peritonitis with antibiotic therapy occurred in only 11% of patients. In the event of a refractory exit site or tunnel infection without associated peritonitis, observational data suggest that simultaneous removal and reinsertion of the PD catheter with a new exit site under antibiotic coverage is an option. Some surgical alternatives for PD catheter salvage in the presence of chronic, refractory exit site and tunnel infections without peritonitis, include unroofing of the infected PD catheter tunnel, partial catheter reimplantation, and catheter diversion procedure with exit site renewal, each with variable success rates. There are also some observational data on the successful use of cuff shaving for nonresolving exit site infection. If a catheter infection occurs simultaneously with a peritonitis episode with the same organism, catheter removal and transfer to hemodialysis are recommended, with the possibility of reinsertion of a new PD catheter at least 2 weeks after catheter removal and resolution of symptoms.

The relationship between exit site infection and the risk of subsequent peritonitis has been investigated in several studies. In 2013, a qualitative review of nine such studies was performed, with eight of the nine studies suggesting that a history of exit site infection was associated with a higher risk of subsequent peritonitis, although evidence for a causal link was not present. In the most recent of these studies, it was found that having an exit site infection was associated with a sixfold higher risk of developing peritonitis within 30 days, even if the exit site infection was appropriately treated. The highest risk was early on, and it diminished

with time. Interestingly, the subsequent peritonitis was only rarely caused by the same organism as the previous exit site infection, suggesting that either high-risk patient characteristics, the immune response to the exit site infection, or the use of antibiotics to treat it may have contributed to the subsequent increased risk of peritonitis.

Prevention

Since some exit site and tunnel infections can be hard to eradicate, the best strategy is prevention. Preventive strategies that can reduce the frequency of PD-associated exit site and tunnel infections can be divided into appropriate early peri-implantation care and proper long-term exit site care.

At the time of PD catheter insertion, there are several important considerations. First, the selection of the exit site location is critical. While most exit sites are located in the lower abdomen, consideration should be given to upper abdominal or presternal exit sites in the presence of a stoma or obesity with a large pannus. Furthermore, special attention should be paid to avoid placement of the exit site at the level of the patient's belt line. In all cases, the exit site should be visible to the patient so as to optimize long-term catheter care and early identification of changes in the appearance of the exit site. The superficial catheter cuff should be located approximately 2–3 cm deep to the exit site in order to avoid extrusion of the cuff, which can irritate the exit site and augment the risk of infection. The placement of an anchoring stitch or sutures at the exit site should be avoided, as this may serve as an unnecessary nidus for infection. Once the catheter is placed, a semiocclusive dressing should be used, and this dressing should not be removed or manipulated for the first week after catheter placement unless the dressing becomes soaked. Avoidance of frequent early dressing changes can help to prevent the introduction of organisms at the exit site. In addition, this will minimize trauma and catheter movement, such that healing and epithelialization of the tunnel tract will be optimized. The catheter should be properly stabilized on the skin in order to minimize the mechanical stress transmitted to the exit site and tunnel, particularly during the healing period. If a PD catheter is being implanted well in advance of the expected date of use, embedding the catheter below the surface of the skin with exteriorization, only at the time of PD initiation, is another strategy that may minimize the risk of infection; although, the evidence to support this strategy for infection prevention is inconclusive. It is unclear whether preoperative antibiotics reduce the risk of exit site and tunnel infections after catheter implantation, but they have been shown to be associated with a lower risk of peritonitis in the postimplantation period and are therefore recommended. No technique of catheter placement (e.g., surgical vs. interventional, laparoscopy vs laparotomy) has been demonstrated to be superior to another for the prevention of catheter-related infections, nor has any particular catheter design. Optimizing patient training, including the use of an adult learning theory-based curriculum, has been shown to be associated with a lower risk of exit site infection.

Once the exit site is healed, it should be cleansed at least twice weekly and every time after a shower. Several cleansing strategies have been employed, including use of antibacterial soap and water, povidone-iodine, chlorhexidine, and sodium hypochlorite. No studies to date have definitively shown one cleansing strategy to be superior to another.

Based on the finding that *S. aureus* nasal carriage increases the risk of *S. aureus* exit site infection and peritonitis, one of the most studied strategies to prevent exit site infection involves the eradication of *S. aureus* colonization. The first agent used for eradication of *S. aureus* nasal carriage was oral rifampin for 5 days of every month, and while this strategy was effective, the routine use of this drug was limited by side effects, drug interactions, and the risk of developing resistance to rifampin over time. A more favorable strategy was identified in the form of mupirocin, a topical agent known to have excellent antibacterial activity against Gram-positive organisms, including *S. aureus*. Several studies have reported on the use of topical mupirocin, either intranasally in *S. aureus* carriers or at the exit site in all PD patients and have shown a significant reduction in the risk of *S. aureus* exit site infection and peritonitis. Despite some reports of the development of mupirocin resistance over time, the widespread adoption of mupirocin prophylaxis led to a dramatic decrease in the frequency of *S. aureus* exit site infection.

While the risk of *S. aureus* exit site infection and peritonitis declined significantly with the advent of strategies targeting *S. aureus* colonization, the risk of *Pseudomonas* exit site infection over the same time period did not change. This led to the idea that topical gentamicin, an agent with antibacterial activity against both Gram-positive and Gram-negative organisms, might provide further benefit over mupirocin. In a multicenter randomized trial published in 2005, exit site application of topical mupirocin and gentamicin was compared, and it was found that while both were very effective at reducing Gram-positive exit site infection, topical gentamicin was superior in the prevention of Gram-negative exit site infection and peritonitis. However, several subsequent observational studies have not been able to confirm the superiority of gentamicin over mupirocin. In addition, one study reported a higher risk of exit site infection caused by certain Gram-negative organisms with gentamicin use, and another study raised the possibility that gentamicin might be associated with a higher risk of exit site infection caused by atypical mycobacteria. Two subsequent randomized trials of other exit site strategies have been published. In one trial in which Polysporin triple ointment was compared with mupirocin, the Polysporin triple ointment was not shown to be superior, and there was a higher risk of fungal exit site infection. In the second trial, exit site application of antibacterial honey in all patients was compared to intranasal mupirocin in *S. aureus* carriers, but there was an increased risk of infection among diabetic patients in the antibacterial honey group.

Based on the previous findings, the 2017 ISPD catheter-related infection recommendations include the use of daily topical application of antibiotic cream or ointment to the catheter exit site. The guidelines state that no cleansing agent has been shown to be superior with respect to preventing catheter-related infections. Since the choice of the topical agent is left to the discretion of the clinician, it should ideally be based on local patterns of infection (including the frequency of *Pseudomonas* catheter infections) and local antibiotic resistance. For patients colonized with methicillin-resistant *S. aureus*, mupirocin should be the topical agent of choice. The final point is that while most PD catheters are made of silicone, topical mupirocin ointment (as opposed to mupirocin cream) should not be used at the exit site of polyurethane catheters due to the potential for structural damage to the catheter over time.

Summary

While exit site and tunnel infections tend to be less common than peritonitis in most PD programs, they remain important complications of PD. Early diagnosis and appropriate treatment are critical in order to improve the likelihood of resolution of the infection. Despite optimal care, some severe catheter infections require removal of the PD catheter. Several preventive strategies have been shown to reduce the risk of exit site and tunnel infection.

Recommended Reading

Bernardini J, Bender F, Florio T, et al. Randomized double-blind trial of antibiotic exit site cream for prevention of exit site infection in peritoneal dialysis patients. *J Am Soc Nephrol.* 2005;16(2):539–545.

This randomized trial compares the use of topical gentamicin and mupirocin at the PD catheter exit site.

Luzar MA, Coles GA, Faller B, et al. *Staphylococcus aureus* nasal carriage and infection in patients on continuous ambulatory peritoneal dialysis. *N Engl J Med.* 1990;322:505–509.

This study demonstrates the important link between S. aureus nasal carriage and subsequent development of exit site infection and peritonitis.

Mujais S. Microbiology and outcomes of peritonitis in North America. *Kidney Int Suppl.* 2006;70:S55–S62.

This report describes the microbiology of exit site infection and peritonitis in a large North American cohort of PD patients.

Mupirocin Study Group. Nasal mupirocin prevents *Staphylococcus aureus* exit-site infection during peritoneal dialysis. *J Am Soc Nephrol.* 1996;7(11):2403–2408.

This randomized trial demonstrates the effectiveness of intranasal mupirocin for the prevention of S. aureus exit site infection among S. aureus nasal carriers.

Strippoli GF, Tong A, Johnson D, et al. Antimicrobial agents for preventing peritonitis in peritoneal dialysis patients. *Cochrane Database Syst Rev.* 2004;18(4).

This systematic review summarizes the data on the use of various antimicrobial strategies for the prevention of exit site infection and peritonitis.

Szeto CC, Li PK, Johnson DW, et al. ISPD catheter-related infection recommendations: 2017 update. *Perit Dial Int.* 2017;37(2):141–154.

This document highlights the ISPD recommendations for prevention, diagnosis, and management of catheter-related infections.

Twardowski ZJ, Prowant BF. Current approach to exit site infections in patients on peritoneal dialysis. *Nephrol Dial Transplant.* 1997;12:1284–1295.

This report discusses some practical aspects regarding exit site healing and chronic PD catheter care.

van Diepen AT, Jassal SV. A qualitative systematic review of the literature supporting a causal relationship between exit-site infection and subsequent peritonitis in patients with end-stage renal disease treated with peritoneal dialysis. *Perit Dial Int.* 2013;33(6):604–610.

This study reviews several studies that have sought to determine the relationship between exit site infection and subsequent development of peritonitis.

27

Peritonitis in Peritoneal Dialysis

CHEUK-CHUN SZETO, MD, FRCP

Peritoneal dialysis (PD) is the modality of kidney replacement therapy in about 15% of the dialysis population worldwide. Despite the advances in technology and antibiotic therapy, peritonitis remains a major cause of technique failure and morbidity in PD patients. Although only 4% of peritonitis episodes are a direct cause of mortality, peritonitis is a contributing factor to death in 16% of PD patients. Furthermore, peritonitis accounts for 30% of PD technique failure and 15% to 35% of patient hospitalization.

Reporting of Peritonitis Rate

Peritonitis rates should be reported as number of episodes per patient-year rather than as the interval in months between episodes. Every PD program should monitor the peritonitis rate at least yearly. In addition to the overall peritonitis rate, other parameters that could be considered for regular monitoring include peritonitis rates of specific organisms, the percentage of patients per year who are peritonitis free, and the antimicrobial susceptibilities of the infecting organisms. Some centers also monitor the incidence of death associated with peritonitis, which is often defined as death with active peritonitis or within 4 weeks of a peritonitis episode, or any death during the hospitalization for a peritonitis episode.

There are substantial variations in the peritonitis rate between countries as well as between different centers of the same country, but a reasonable target for any PD center should be within 0.5 episodes per year of treatment. Many centers now report a peritonitis rate of 0.2 to 0.3 episodes per year of treatment.

Risk Factors

The risk factors for peritonitis include patient, technique, and environment related (Table 27.1). However, although many risk factors listed in Table 27.1 are labeled as "modifiable," there is often a lack of published evidence that modifying these risk factors would reduce peritonitis rates. There is a strong association between PD catheter-related infections (either exit site or tunnel infection) and subsequent peritonitis. Early detection of and prompt antibiotics therapy for catheter-related infections are important steps to reduce the risk of peritonitis.

Older patients are at risk, but patients below 20 years of age also have higher risk than middle-aged ones. The socioeconomic status of patients is associated with peritonitis risk. Patients with fewer than 9 years of education have twice as high a peritonitis rate compared to those with over 12 years of education. Depression (e.g., as indicated by a Beck Depression Inventory score) is also associated with the risk of peritonitis.

PD patients with diabetes are at particularly high risk for peritonitis because of multiple mechanisms. Diabetes adversely affects peritoneal defense mechanisms by interfering with the migration of phagocytic cells into the peritoneum. Formation of advanced glycation end products further suppresses the phagocytic activity of resident peritoneal macrophages. Impaired vision and dexterity increase the risk of touch contamination. Concomitant autonomic neuropathy results in a decrease in intestinal motility or slow colonic transit time, which favors bacterial overgrowth and increases the risk of peritonitis due to enteric organisms.

Patients with *Staphylococcus aureus* nasal carriage have a higher risk for *S. aureus* peritonitis. Intranasal mupirocin ointment reduces *S. aureus* exit site infections but is less effective in preventing peritonitis. Intermittent nasal mupirocin application may further prevent redevelopment of *S. aureus* carriage, and the incidence of antibiotic resistance does not seem to be increased.

Several reports suggest a seasonal variation in the incidence of PD-related peritonitis, with peak incidence in the months that are hot and humid. Keeping a cool and dry living environment may reduce the risk of peritonitis, particularly in tropical countries.

Pathogenesis and Causative Organisms

Bacteria could invade the peritoneal cavity through several routes: intraluminal (via touch contamination during PD exchange), periluminal (as a result of catheter-related

TABLE 27.1 Risk Factors for Peritonitis

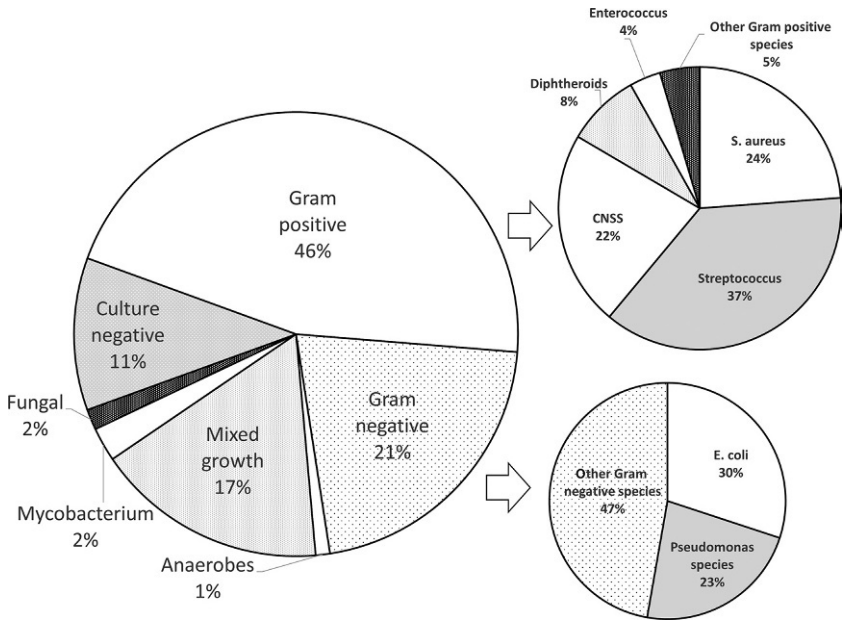
	Nonmodifiable	Modifiable
Patient related	• Older age • Female • Black race • Lower socioeconomic status • Diabetes mellitus • Coronary artery disease • Chronic lung disease • Hypertension • Poor residual kidney function	• Obesity • Smoking • Depression • Hypoalbuminemia • Hypokalemia • Medical procedures • No vitamin D supplement • Bioincompatible fluids • Nasal *Staphylococcus aureus* carrier • Previous exit site infections
Technique related	• Center effect	• Method of patient training • Connecting system • Prophylactic antibiotics for nasal carriage • Prophylactic antibiotics for exit site care
Environment related	• Hot and humid climate	• Living distantly from dialysis unit • Pets

infections), intestinal (via transmural spread through the bowel wall), systemic (secondary to septicemia or hematogenous spread), and rarely ascending (through the vagina).

The causative organism can be isolated from the PD effluent in over 90% of peritonitis episodes using appropriate culture techniques. With the extensive use of the "flush before fill" technology and double-bag disconnect systems, Gram-positive and Gram-negative organisms accounted for about 40% and 30% of all peritonitis episodes, respectively (Fig. 27.1). Among the Gram-negative organisms, the Enterobacteriaceae family, which is often labeled as "enteric bacteria," is the most common. However, there are substantial variations in the prevalence of individual organisms as well as the spectrum of antibiotic resistance between different centers. Each PD unit should take note of its own local data in order to design the optimal management and quality-improvement strategies.

Diagnosis

From a case-reporting point of view, the diagnosis of PD-related peritonitis is confirmed when at least two of the following conditions are present: (1) symptoms and signs of peritoneal inflammation; (2) cloudy PD effluent with an elevated leukocyte count (> 100/μL) or neutrophil



• **Fig. 27.1** Causative organisms of peritoneal dialysis–related peritonitis in Prince of Wales Hospital from 2010 to 2019. *CNSS*, Coagulase negative staphylococcal species; *S. aureus, Staphylococcus aureus*.

predominance (>50%) in the PD effluent; and (3) presence of bacteria in the PD effluent by Gram stain or culture. In clinical practice, however, PD patients presenting with cloudy effluent should be presumed to have peritonitis. It is important to initiate empiric antibiotic therapy in these patients as soon as possible. There are other causes of cloudy peritoneal effluent (e.g., chemical peritonitis, eosinophilia of the effluent, hemoperitoneum, and rarely, malignancy and chylous effluent), but the risk of serious consequences of peritonitis (i.e., relapse, catheter removal, permanent transfer to hemodialysis, and death) are much higher if treatment is not promptly initiated. Although a number of novel diagnostic techniques have been explored, there is insufficient evidence to recommend their routine clinical use.

Clinical Assessment

Assessment of the patient should include history taking for possible touch contamination, adherence with sterile dialysis technique, recent invasive procedures that may have led to peritonitis, and change in bowel habits (either diarrhea or constipation). Physical examination should focus on abdominal and vital signs. The presence of features that suggest systemic sepsis (i.e., high fever or hypothermia, hypotension, tachycardia, tachypnea, or altered mental state) would favor the use of intravenous instead of intraperitoneal antibiotic therapy. Catheter exit site and tunnel should be examined for features of concomitant catheter-related infections, which may be the cause of the peritonitis.

Microbiological Investigations

The diagnosis of peritonitis and the subsequent management of PD-related peritonitis depends on a timely specimen collection with the appropriate technique. After the initial clinical assessment, PD effluent should be obtained before the addition of antibiotics, and the specimen should be sent immediately to the laboratory for absolute cell count and differential counts as well as bacterial culture. If the specimen is collected after rapid PD cycles (with a dwell time less than 2 hours), the percentage of neutrophils rather than the total leukocyte cell count should be used for the diagnosis of peritonitis.

PD effluent cell count is important because it can differentiate cellular elements of the peritonitis from other causes of cloudy PD effluent (e.g., fibrin, chyle). Most of the leukocytes in the PD effluent of untreated peritonitis should be neutrophils or lymphocytes. A high proportion of eosinophils should raise the suspicion of allergic peritonitis, which usually happens soon after starting PD due to allergy to plasticizers. Tuberculous peritonitis should be suspected if there is a predominance of lymphocytes or macrophages in the PD effluent. It should be noted that cell lysis may occur after 24 to 48 hours of specimen collection, and the cell morphology would not be identified if specimen handling is delayed.

Traditionally, PD effluent is collected in universal sterile bottles for bacterial culture. The fluid specimen is centrifuged, and the sediment is used for Gram stain and plate culture. However, the yield of this method is low. The latest International Society for Peritoneal Dialysis (ISPD) guidelines recommend the use of blood-culture bottles for the bacterial culture of PD effluent because nutrients inside this system facilitate the growth and identification of any causative organism. If immediate delivery to the laboratory is not possible, the inoculated culture bottles should be incubated at 37°C. Centrifugation of a large volume of PD effluent (e.g., 50 mL) followed by resuspension of the sediment and inoculation in the standard blood culture media further increases the yield by 5 to 10 times, but the technique is cumbersome. Blood cultures are not necessary unless there is clinical suspicion of systemic sepsis.

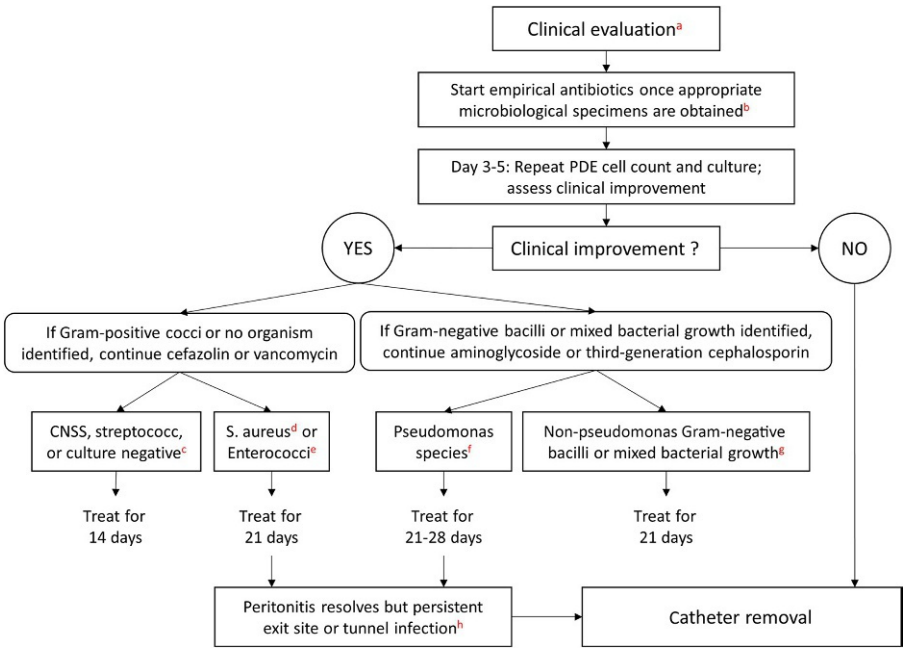
Management

Patients presenting with cloudy PD effluent should be presumed to have peritonitis, and empiric antibiotic therapy should be started once appropriate microbiological specimens have been obtained, and there is no need to wait for the result of any laboratory test. The latest ISPD guidelines recommend center-specific selection of empiric antibiotic regimens that cover both gram-positive and gram-negative organisms. In general, Gram-positive organisms may be covered by vancomycin or a first-generation cephalosporin, while Gram-negative organisms may be covered by aminoglycoside or a third-generation cephalosporin. The choice should depend on the local antibiotic sensitivity of individual PD centers.

Fig. 27.2 summarizes the overall management algorithm of PD-related peritonitis. The authors favor cefazolin over vancomycin for Gram-positive coverage so as to minimize the risk of the emergence of vancomycin-resistant organisms. Although short-term aminoglycoside therapy is safe and provides good Gram-negative coverage, repeated or extended courses of aminoglycoside should be avoided because of the risk for both vestibular toxicity and ototoxicity.

Antibiotic Administration

If the patient has clinical features of systemic sepsis, antibiotics should be administered intravenously in addition to other resuscitative measures. Otherwise, intraperitoneal administration of antibiotics is superior to intravenous dosing for PD-related peritonitis. The latest ISPD guideline on intraperitoneal antibiotic dosing recommendations is summarized in Table 27.2. It is important to note that the stated dosages are primarily recommended for patients receiving continuous ambulatory PD (CAPD). If there is substantial residual kidney function (e.g., residual glomerular filtration rate ≥ 5 mL/min/1.73 m^2), the dose of antibiotics may need to be adjusted accordingly.



• **Fig. 27.2** Management algorithm of peritoneal dialysis-related peritonitis. [a]Clinical evaluation includes routine history, physical examination, examination of the exit site and catheter tunnel, collection of PDE for cell count, differential count, Gram stain, and bacterial culture. [b]The choice of empirical antibiotics coverage should be based on patient history and center sensitivity patterns; also consider adjuvant treatment: pain control, intraperitoneal heparin, and antifungal prophylaxis. [c]If the risk of Gram-negative peritonitis is high (by local epidemiology or patient-related factors), empirical Gram-negative coverage may be continued for culture-negative episodes. [d]Screen for *S. aureus* carrier. [e]Use vancomycin or other appropriate agents because *Enterococci* has intrinsic resistance to cefazolin. [f]Give two effective antibiotics according to sensitivity; also applicable to *Stenotrophomonas* and other *Pseudomonas*-like species. [g]Consider surgical problem; consider addition of metronidazole and vancomycin. [h]Simultaneous removal and reinsertion of a new catheter may be possible. *CNSS*, Coagulase negative staphylococcal species; *PDE*, peritoneal dialysis effluent; *S. aureus, Staphylococcus aureus*.

Intraperitoneal antibiotics can be given in each exchange as continuous dosing or once daily as intermittent dosing, and both are equally efficacious. In intermittent dosing, the antibiotic-containing dialysis solution must be allowed to dwell for at least 6 hours to allow adequate absorption of the antibiotic into the systemic circulation. Once-daily therapy has the advantage of ease of use. In addition, once-daily dosing of aminoglycosides may result in less ototoxicity and nephrotoxicity. Evidence supports good efficacy of intermittent dosing of aminoglycosides and vancomycin. On the other hand, data in support of intermittent dosage of cephalosporin are less complete, and continuous administration should be the recommended approach unless it is not practically feasible.

Special Considerations in Automated Peritoneal Dialysis

The choice of first-line antibiotics in PD applies to both CAPD and automated PD (APD). Nonetheless, the recommendations for antibiotic treatment are based mainly on data obtained in CAPD, and experience in APD is often limited. From a practical point of view, it is often more convenient to administer the loading dose intravenously for APD patients. For APD patients with a daytime dwell, antibiotics can be administered conveniently just in the daytime dwell. For patients with no daytime dwell, a daytime dwell could be added, and antibiotics can be administered into the daytime dwell. Alternatively, temporary conversion to a CAPD regimen may be considered. However, this approach is possible only if the patient has additional training and suitable stock of PD solutions, and it may result in fluid retention in people with fast peritoneal transfer rates.

Adjunctive Treatment

Since most of the fungal peritonitis episodes are preceded by the use of antibiotics, antifungal prophylaxis should be used while PD patients are receiving antibiotic therapy. In general, oral nystatin is the recommended approach for antifungal prophylaxis. Fibrinous clots are commonly found in PD effluent during peritonitis, and there is a risk of catheter obstruction. Heparin (500–1000 units/L) is often added to the dialysis solution until the PD effluent clears up. Urokinase has been used by some investigators in the treatment of refractory or relapsing peritonitis. In theory, fibrinolytic treatment could release bacteria entrapped in biofilm within the peritoneum or along the catheter, thus making it possible to eradicate the infection. However, studies of intraperitoneal urokinase show conflicting results, and this treatment is not routinely recommended.

TABLE 27.2 Intraperitoneal Antibiotic Dosing Recommendations

	Intermittent	Continuous (All Exchanges)
Aminoglycosides		
Amikacin	2 mg/kg daily	LD 25 mg/L, MD 12 mg/L
Gentamicin	0.6 mg/kg daily	LD 8 mg/L, MD 4 mg/L
Netilmicin	0.6 mg/kg daily	MD 10 mg/L
Tobramycin	0.6 mg/kg daily	LD 3 mg/kg, MD 0.3 mg/kg
Cephalosporins		
Cefazolin	15–20 mg/kg daily	LD 500 mg/L, MD 125 mg/L
Cefepime	1000 mg daily	LD 250–500 mg/L, MD 125 mg/L
Cefoperazone	No data	LD 500 mg/L, MD 62.5–125 mg/L
Ceftazidime	1000–1500 mg daily	LD 500 mg/L, MD 125 mg/L
Others		
Piperacillin/tazobactam	No data	LD 4.5 gm, MD 1.125 gm
Ciprofloxacin	No data	MD 50 mg/L
Daptomycin	No data	LD 100 mg/L, MD 20 mg/L
Imipenem/cilastatin	500 mg in alternate exchange	LD 250 mg/L, MD 50 mg/L
Ofloxacin	no data	LD 200 mg, MD 25 mg/L
Polymyxin B	no data	MD 300,000 unit (30 mg)/bag
Meropenem	1 gm daily	No data
Vancomycin	15–30 mg/kg every 5–7 days	LD 30 mg/kg, MD 1.5 mg/kg/bag
Antifungals		
Fluconazole	200 mg every 24 to 48 hours	No data
Voriconazole	2.5 mg/kg daily	No data

LD, Loading dose; *MD*, maintenance dose.
Adapted from Li PK, Szeto CC, Piraino B, et al. ISPD peritonitis recommendations: 2016 update on prevention and treatment. *Perit Dial Int*. 2016;36:481–508.

Subsequent Management

With effective treatment, patients should improve clinically within 12 to 48 hours. When culture results and sensitivities are known, antibiotic therapy should be adjusted accordingly (see Fig. 27.2).

Gram-Positive Organism Identified

If *S. aureus*, coagulase-negative *Staphylococcus* species, or *Streptococcus* species are identified from PD effluent, cefazolin or vancomycin treatment should be recommended. Many coagulase-negative *Staphylococcus* species are reported to be resistant to first-generation cephalosporin by laboratory testing but are sensitive to the levels achieved in the peritoneal cavity. Therefore, if the patient is clinically responding to treatment, there is no need to change the antibiotic regimen. Enterococcal peritonitis tends to be severe and, because enterococci have intrinsic resistance to cephalosporin, should be treated with intraperitoneal vancomycin. In general, effective antimicrobial therapy should be continued for 14 days for Gram-positive peritonitis episodes if the improvement is prompt, but episodes caused by *S. aureus* or enterococci require antimicrobials for 3 weeks. Episodes caused by *S. aureus* also require screening for the nasal carrier state. A short course of oral rifampicin as an adjunct may reduce the risk of relapsing or repeat *S. aureus* peritonitis episodes, but the enzyme inducer effect of rifampicin should be considered.

Gram-Negative Organism Identified

If a single, non-*Pseudomonas* organism is identified in the PD effluent, the empirical intraperitoneal third-generation cephalosporin or aminoglycoside should be continued. Treatment should be continued for 21 days. If a *Pseudomonas* or *Stenotrophomonas* species is recovered, then two effective antipseudomonal antibiotics are needed. Suitable choices include aminoglycoside, third-generation cephalosporin, semisynthetic penicillin with antipseudomonal activity

(e.g., piperacillin), fluoroquinolone, aztreonam, imipenem, and trimethoprim-sulfamethoxazole. It should be noted that semisynthetic penicillins can inactivate aminoglycosides in vitro, and these two agents should not be coadministered intraperitoneally. The duration of therapy should be 21 to 28 days. Pseudomonas peritonitis is often related to a catheter infection, and catheter removal is often required.

Culture-Negative Peritonitis

If PD effluent yields no bacterial growth after incubation for 48 to 72 hours, the most common explanations are technical problems during collection of dialysate samples for culture and recent use of antibiotics. If a PD program has a rate of culture-negative peritonitis greater than 20%, the culture methods and logistics should be reviewed and improved. Management depends on whether the patient is improving clinically. If the patient is improving, cefazolin alone should be continued for 2 weeks. However, if the patient shows no improvement, PD effluent culture should be repeated to look for unusual organisms, including fungus and mycobacteria.

Polymicrobial Peritonitis

Management should be individualized. In general, if multiple enteric organisms or anaerobic bacteria are grown, surgical evaluation should be obtained. On the other hand, peritonitis episodes caused by multiple Gram-positive organisms usually respond to antibiotic therapy alone without catheter removal, and surgical evaluation is not routinely required.

Tuberculous Peritonitis

Tuberculosis is an infrequent cause of peritonitis and can be difficult to diagnose. When clinically suspected (e.g., persistent culture-negative peritonitis or lymphocytosis in PD effluent), special attention should be paid to the culture technique. Patients often respond well to standard antituberculous chemotherapy, and catheter removal is often not required if therapy is promptly started. However, streptomycin and ethambutol are generally not recommended in dialysis patients.

Fungal Peritonitis

Fungal peritonitis is a serious complication and should be suspected after recent antibiotic treatment for bacterial peritonitis. Candida is the most prevalent species. Catheter removal is recommended once fungi are identified by microscopy or culture, and antifungal agents should be continued for at least 14 days after catheter removal.

Indications for Catheter Removal

PD catheter should be removed for refractory peritonitis, relapsing peritonitis, fungal peritonitis, and refractory catheter infections. Refractory peritonitis is defined as failure to clear after 4 to 5 days of appropriate antibiotics. The objective of peritonitis treatment is preservation of the peritoneum rather than saving the peritoneal catheter. After catheter removal, systemic antibiotics should be continued for at least 2 more weeks. Reinsertion of a new catheter can be considered 3 to 4 weeks after catheter removal, and all signs of peritonism have disappeared. Resumption of PD is possible in approximately half of the patients, but with ultrafiltration, problems are common.

Relapsing, Recurrent, and Repeat Peritonitis

As stated in the latest ISPD guideline, relapsing peritonitis is defined as an episode that occurs within 4 weeks after completion of therapy of a prior episode with the same organism or with sterile PD effluent culture; recurrent peritonitis is an episode that occurs within 4 weeks after completion of therapy of a prior episode but with a different organism, and a repeat episode is one that occurs more than 4 weeks after completion of therapy of a prior episode with the same organism. They represent distinct entities but generally portend a poor outcome. Timely catheter removal should be considered, especially for relapsing peritonitis episodes. If the PD effluent clears up with antibiotic therapy, it may be possible to insert a new catheter simultaneously with removal of the old catheter.

Predictors of Treatment Failure

Previous studies showed that the number of years on PD, the presence of diabetes mellitus and peritonitis with Gram-negative organisms, fungal, or Mycobacterium species are independent predictive factors of treatment failure. In addition, the PD effluent total white blood cell (WBC) count on day 3 of peritonitis predicts treatment failure in addition to standard risk factors. A PD effluent WBC count of 1090/mm^3 or greater on day 3 has 75% sensitivity and 74% specificity for predicting catheter loss or peritonitis-related death.

Impact of Peritonitis

The permeability of the peritoneum to water, glucose, and proteins is increased during peritonitis. Rapid absorption of glucose from the dialysis solution reduces the amount of ultrafiltration and may result in fluid overload. Higher dialysis solution glucose levels and shorter dwell times may be needed to maintain adequate ultrafiltration. Glycemic control may also worsen in diabetic patients during peritonitis, partly as the result of rapid glucose absorption. Regular blood glucose monitoring and appropriate adjustments of insulin dosage may be needed. In addition, peritoneal protein loss is also increased during peritonitis, and the nutritional status of patients may worsen rapidly.

Peritonitis may also have last effects on the PD patient. An episode of severe peritonitis often results in lasting effects, including a rise in peritoneal permeability to small solutes and loss of ultrafiltration. As discussed previously, only half of the patients could resume PD after an episode of refractory peritonitis and catheter removal, and there is often a substantial decline in the ultrafiltration capacity in these patients that require additional dialysis exchanges or hypertonic cycles to compensate for the loss of solute clearance or ultrafiltration.

Prevention of Peritonitis

Strategies to prevent peritonitis include better patient training, improved exit site care, treatment of *S. aureus* nasal carriage, and antibiotic prophylaxis under appropriate settings. Careful selection of patients could diminish the rate of peritonitis secondary to contamination. The method of training has a substantial influence on the risk of peritonitis, but the critical components of a "good" training program remain poorly defined. In general, PD training should be conducted by nursing staff with the appropriate qualifications and experience, and the latest ISPD recommendations for teaching PD patients and their caregivers should be followed. Each PD program should consult the ISPD guidelines to prepare the trainer and develop a specific curriculum for PD training. Continued monitoring of the peritonitis rate is necessary in all dialysis programs. A high rate of peritonitis in a dialysis center should be followed by a critical appraisal of the pathogenic organisms as well as the training program with appropriate interventions taken. In addition, each PD center should have a continuous quality improvement (CQI) program in place, with an aim to reduce peritonitis rates. A multidisciplinary team that runs the CQI program in PD centers should meet and review their unit's performance metrics regularly.

Systemic prophylactic antibiotics should be administered immediately prior to PD catheter insertion. The usual recommendation is a single intravenous dose of first-generation cephalosporin. Intravenous vancomycin is an effective alternative, but the potential risk of hastening resistant organisms has to be considered. Disconnect systems with a "flush before fill" design for CAPD reduce the risk of peritonitis caused by Gram-positive organisms and has become the standard of practice. The design of PD catheter, insertion technique, and the choice of PD solution does not seem to significantly affect the risk of peritonitis.

Peritonitis episodes are frequently preceded by exit site or catheter infections, which should be treated promptly once recognized. Good exit site care helps in preventing catheter infections and peritonitis. The latest ISPD guidelines recommend daily topical application of antibiotic (mupirocin or gentamicin) cream or ointment to the catheter exit site. For routine exit site care, there are sufficient data to support the use of PD catheter exit site antibiotic creams (either mupirocin or gentamicin). Mupirocin ointment applied daily to the exit site decreases the rate of both exit-site infections and peritonitis, and resistance does not appear to be a major problem despite prolonged use. Some studies showed that gentamicin cream was as effective as mupirocin in preventing *S. aureus* infections, and gentamicin cream also reduces catheter infections caused by Gram-negative organisms. However, the incidence and implications of gentamicin resistance are uncertain. Nasal carriage of *S. aureus* has been associated with a higher risk of PD catheter infections and peritonitis, and the risk may be reduced with eradication therapy. Intranasal topic mupirocin and oral rifampin could have both been reported to be effective for eradication, but topical mupirocin is preferred. The optimal protocol for regular screening of nasal S. aureus carriers, and treatment of relapse is, however, not well defined.

In addition to prophylactic antibiotics prior to PD catheter insertion, short-term prophylactic antibiotics are beneficial before invasive procedures, particularly colonoscopy, hysteroscopy, or cholecystectomy, and after wet contamination. However, the benefit of prophylactic antibiotics before other simple procedures (e.g., dental extraction, upper gastrointestinal endoscopy) is controversial.

Secondary prevention is also important. As discussed earlier, antifungal prophylaxis to prevent secondary fungal (mostly Candida) peritonitis should be given when PD patients receive antibiotic treatment for an episode of bacterial peritonitis. Antifungal prophylaxis may also reduce the risk of fungal peritonitis when a PD patient receives systemic antibiotics for nonperitonitis infections, but this practice is not widely adopted. After each peritonitis episode, it is prudent to perform a root-cause analysis to determine the etiology so that interventions can be planned to prevent future episodes. Although published data are limited, retraining should be considered after peritonitis or a change in the dexterity, vision, or mental acuity of the patient.

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This is an update and elegant review on the risk factors, treatment, and prevention of PD peritonitis.

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Abdominal Hernias With Peritoneal Dialysis

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Complications related to peritoneal dialysis (PD) can be categorized as infectious or noninfectious. Noninfectious complications, including abdominal hernias, catheter malfunction, and exit site leaks, occur in continuous ambulatory PD (CAPD), continuous cycling PD/automated PD (CCPD/APD), and intermittent PD (IPD). More serious complications, such as catheter erosion into the bowel, bladder, or vagina, are rare and related to the presence of a catheter irrespective of the form of PD used.

Abdominal hernias are the most common of the anatomic complications of PD and contribute significantly to morbidity, increased medical costs, and withdrawal from PD.[1]

Incidence and Prevalence

The prevalence of PD-related hernias ranges from 7% to 25% based on a number of completed studies.[2] However, the incidence of hernias has dropped from 0.21 hernias per PD-year at risk since the early 1980s to about 0.06 hernias per PD-year at risk in late 1990s.[3,4] This finding may be attributable to the discontinuation of midline catheter insertions and resorbable suture material. Emerging evidence demonstrates a further decline in the incidence of hernias, with 0.04 hernias per PD-year at risk being reported in 2014.[5]

Types of Abdominal Wall Hernias

Several locations of hernia formation have been described in patients undergoing PD, including inguinal, catheter exit site, umbilical, incisional, ventral, epigastric, pelvic, femoral, and obturator. Although the prevalence rates vary in the literature, the most commonly occurring hernias are inguinal hernias. They account for 75% of abdominal wall hernias. Indirect inguinal hernia was more frequent in PD patients than in hemodialysis (HD) patients due to the internal ring expansion via an increase of intra-abdominal pressure from peritoneal dialysate.[6]

Hernial sacs may contain subcutaneous fat, bowel, or peritoneal fluid (or a combination). Unusual hernias such as spigelian, Ritchers, foramen of Morgagni or diaphragmatic, rectocele, cystocele, and uterine prolapse have also been reported in the PD population.

Risk Factors

Normal intra-abdominal pressure in an empty peritoneal cavity is about 0.5 to 2.2 cm H_2O, which increases to nearly 2 to 10 cm H_2O with instillation of dialysate volumes commonly used in clinical practice. The increase in intra-abdominal pressure is linearly correlated to the volume of dialysate instilled. Therefore, a theoretical association between larger dialysate volumes and intra-abdominal pressure and risk of hernia exists, but supportive evidence in the literature is lacking.[7–9] Factors that may contribute to higher intra-abdominal pressure include coughing or straining, which can transiently elevate abdominal pressure to as high as 120 to 150 cm H_2O, with varying volumes of intraperitoneal dialysate.[10]

The PD modality may possibly influence hernia formation based on the presumptive principle that intra-abdominal pressures are lower during recumbency compared with the ambulatory state. In IPD, the patient remains supine throughout the treatment, which attenuates the rise in intra-abdominal pressure. In CCPD, patients maintain a full volume in their abdominal cavity throughout the day, but the bulk of their treatment occurs during the night while the patient is in the recumbent position. In contrast, patients undergoing CAPD perform dwells and drains during the day. Mean intra-abdominal pressure increases of 2.0, 2.7, and 2.8 cm H_2O per liter of instilled dialysate volume have been demonstrated in supine, upright, and sitting positions, respectively.[10] However, evidence in the literature is inconclusive. A survey of 75 randomly selected dialysis units in the United States and Canada involving 1864 PD patients found no difference in hernia incidence among the various PD modalities (CAPD, APD, and nocturnal IPD).

The association of PD modality and hernia risk was lacking in a study of 47 APD and 14 CAPD patients.[11] However, the rate of hernia was higher but not statistically significant among CAPD patients versus CCPD patients in a 5-year retrospective review from Spain.[8]

Each year on PD increases the risk of hernia formation by 20%.[12] PD duration is, therefore, an important risk factor for hernia formation.[5] Additional risk factors associated with hernia include acquired focal abdominal wall weakening caused by previous abdominal surgery or multiparous status and older age.[13] The rate of hernia formation was statistically significantly higher in patients with a history of hernia or abdominal surgery.[14] Recent abdominal surgery is a relative contraindication for the initiation of PD due to the risk of hernia or leak at the healing incision site.[1,5] Studies suggest that gender may be associated with the development of hernia in the PD population, but they are largely inconclusive. A study done in 2005 suggested that females had a higher risk for developing hernias. More recent data (2014) suggested that females had lower risk for development of hernias.[15] One possible explanation is that male patients are more likely to engage in more exertional labor, thus increasing intra-abdominal pressure.[2] The suggestion that small body size[16,17] is associated with higher risk for hernia formation has not been confirmed in recent studies.[1,11] Among adults in the United States, being overweight and obese was associated with a lower incidence of inguinal hernia.[6] This is supported by a study that found that PD patients weighing less than 90 kg had a higher risk for hernia development versus those weighing more than 90 kg.[18] A lower rate of hernia formation was evident with a weekly Kt/V greater than two compared with a weekly Kt/V less than two.[1] Although constipation is common and could significantly increase intra-abdominal pressure during straining, its contribution to risk of hernia formation in the PD population has not been defined.

There is no correlation between the etiology of kidney disease and development of hernia, with the exception of polycystic kidney disease (PKD). The large size of polycystic kidneys may contribute to increased intra-abdominal pressure by limiting peritoneal space. Alternatively, a PKD-associated generalized collagen disorder may predispose to hernia formation. The collagen defect has been postulated to explain the kidney and liver cysts that develop in PKD, as well as the higher incidence of diverticulosis, valvular defects, and aneurysms. Although the risk for hernia formation is higher in the PKD population undergoing PD, the overall survival rate and peritonitis risk remain comparable to that of nondiabetic PD patients.[19] PKD is not a contraindication for PD therapy.

No correlation has been identified with the type of catheter used[1] or with the type of incision (midline vs. paramedian transrectus), although a paramedian transrectus incision has been suggested as a means of decreasing the incidence of incisional hernias.[20,21] Moreover, paramedian incisions are associated with fewer early postoperative complications and longer PD catheter survival.[22] Similar incidences of hernia development have been associated with open versus laparoscopic PD catheter insertion approaches.[23]

Recent findings suggest that there is an association with a higher residual volume in PD and hernia formation. High-risk patients are advised to reduce their tolerated pressure to 13 cm H_2O to avoid mechanical problems that affect the abdominal walls.[24]

Metabolic factors that influence the formation of abdominal hernias in PD patients include uremia, anemia, obesity, and protein-energy wasting. Additional associated metabolic factors include transperitoneal protein loss and certain medications involved in the wound healing process.[25]

Complications

Untreated hernias may cause cosmetic concerns, discomfort, or loss of ultrafiltration or lead to bowel incarceration and strangulation. Umbilical hernias have a high likelihood of incarceration, strangulation, and recurrence.[16,26] Strangulated hernial sacs predisposed to peritonitis. Early detection of hernias may be difficult; therefore, it is common for patients to present with acute incarceration requiring emergent surgery. Even when a hernia is recognized early, its correction requires hospitalization and interruption of PD therapy, contributing to morbidity, cost, and patient inconvenience. The development of hernias, particularly recurrent hernias, is, therefore, a significant factor influencing a permanent switch to HD.

In addition, the dialysate may leak into the soft tissues if there is a break in the supporting structures of the abdominal wall with hernia formation.

Diagnosis and Management

Most hernias are asymptomatic but may be appreciated on a thorough physical examination. Although in certain cases, however, an examination may not be enough to detect a subclinical hernia. Both advanced magnetic resonance and computed tomography peritoneographic procedures allow direct visualization of the dialysate leakage and a peritoneal hernia. Due to their accuracy, they can be utilized as diagnostic tests. Other alternative procedures that can be used to evaluate PD-related complications are peritoneal scintigraphy, magnetic resonance imaging ultrasonography, as well as barium studies.[27] Because of complications associated with hernia development, timely surgical repair of a hernia is recommended despite somewhat higher 30-day mortality, morbidity, and requirement for reoperation that have been observed in dialysis patients undergoing elective ventral hernia repair.[28] Conventional hernia repair consists of suture closure of the abdominal wall defect and is associated with a recurrence rate of 22% to 29%.[16,29,30] Nowadays, hernioplasty is performed using a prosthetic mesh as a low-tension or tension-free repair to reduce the risk of recurrence. It comprises an underlay patch that provides reinforcement

from inside of the abdominal wall, a connector, and an onlay patch that lies over the abdominal wall. In addition, low tension mesh repair of hernia allows rapid resumption of PD.[31]

Continuation of Peritoneal Dialysis after Hernioplasty

Recent studies recommend the continuation of PD following hernia repair. However, a temporary transfer to HD should be considered if the hernia was associated with bowel incarceration and strangulation to prevent peritonitis.[25] After hernioplasty, the patient can continue with initially low-volume PD with frequent exchanges and then gradually increase the volume, or nighttime CCPD. It is important to follow this protocol to allow incisional wounds to heal efficiently for at least 2 to 4 weeks. The presence of uremia will require a longer healing timeframe.[25] Tension-free hernia repair with a reinforced propylene mesh allowed the patients to continue PD as early as 24 hours after surgery.

In one series, early postoperative dialysis was not necessary in 26 of 49 PD patients who underwent hernia repair, and only 7 patients required temporary HD.[32] In other reported series, the immediate resumption of PD after hernia repair has been successful without giving rise to early hernia recurrence or leakage.[31,33–35]

Another protocol sets up a standard PD therapy until the morning of the surgery, followed by no dialysis for the first 48 hours and IPD three times per week (1 L exchange for 10 hours) for 2 weeks, followed by a low-volume CAPD for 2 weeks, and lastly, the resumption of preoperative PD prescription after 4–5 weeks.[35]

An alternative PD management protocol has been suggested in which low-volume APD exchanges were used starting at an initial fill volume of 1 L. By the second week, the volume was gradually increased to 1.5 L, and the usual dialysis regimen was ultimately resumed thereafter.[33]

Prophylactic Measures

Prophylactic measures to prevent hernia formation in the CAPD population have been suggested but have not been established. The simultaneous repair of preexisting hernias during PD catheter placement is highly recommended in order to decrease the incidence of hernia complications.[16,25,30,35a,36a]

A paramedian transrectus incision may decrease the incidence of incisional hernias at the site of catheter insertion.[20,21] Administration of antitussives and laxatives when indicated may be useful. It is advisable to refrain from vigorous physical activities with a full peritoneal cavity.

Placement of the catheter by an experienced operator and choice of technique are crucial in the prevention of hernias. For example, patients with a history of abdominal surgeries or an ostomy may require a presternal catheter.[36,37]

The incidence of hernia recurrence is approximately 25% after surgical repair.[16,29,30] A reinforcing prosthetic polypropylene mesh may prevent local recurrence by guarding against increased abdominal wall tension. Indeed, prosthetic mesh reinforcement overlying the abdominal wall has been effective in preventing hernia recurrence during a follow-up of 2 to 45 months.[38] In a small retrospective analysis of CAPD patients with large or multiple abdominal hernias who were not candidates for HD, placement of a polypropylene mesh at the time of hernia repair was reported to prevent hernia recurrence.[39] In addition, there was a lower incidence of peritonitis after mesh placement compared with before mesh placement. Extraperitoneal placement or neoperitonealization of the mesh may reduce the risk of secondary mesh infection.[31,40] Failure of mesh hernia repair is rare but has been reported in the setting of unusual comorbidities.[41]

There is no evidence that abdominal binding or the wearing of a corset will, in any way, decrease the incidence of hernia development. APD with low daytime dialysate volume may be recommended for patients at risk of recurrent hernia based on the principle of lower intra-abdominal pressures during recumbency.[8,42]

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Dialysate Leaks with Peritoneal Dialysis

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Introduction

Dialysis fluid leakage is a noninfectious complication of peritoneal dialysis, with reported incidence rates varying from 1% to 40%. Leaks are the result of egress of peritoneal dialysis fluid from the peritoneal cavity through defects created either during the catheter insertion process itself or through congenital or acquired defects in the peritoneal dialysis space. Peritoneal dialysis fluid leaks can result in patients needing corrective surgical procedures, changes in peritoneal dialysis therapy, or possibly necessitating temporary or permanent transition to hemodialysis. Therefore, identification of patients at risk of complications, optimization of catheter break-in, and prompt identification and management of complications are necessary for patients on peritoneal dialysis.

Generally, peritoneal dialysis leaks are classified into early leaks, those occurring within the first 4 weeks of peritoneal dialysis, and late leaks, those occurring after the first 4 weeks following peritoneal dialysis initiation. The most common type of early leak is a pericatheter leak, whereas late leaks tend to consist more of abdominal wall leaks, retroperitoneal leaks, genital edema, or hydrothorax, the latter being discussed more fully in Chapter 30. This temporal classification is not exclusive, however, and any type of leak may present at any given time. Several risk factors exist that may predispose a patient to leaks and are listed in Table 29.1.

Pericatheter Leaks

Pericatheter leaks are one of the most prevalent types of leaks presenting in the early setting after peritoneal dialysis catheter insertion. These leaks commonly present clinically with persistent nonsanguineous drainage around the exit site, soaking through the surrounding dressing. Confirmation of the fluid as being dialysate can be done by having the fluid tested with a standard urine dipstick, which should come back highly positive for glucose, given the composition of most frequently used dialysates. Should this initial test be uncertain, a computed tomography (CT) peritoneogram can be performed to confirm the etiology of the fluid.

The etiology of pericatheter leaks stems from the dialysis fluid tracking along the surgical tunnel used to insert the peritoneal dialysis catheter. Therefore, optimal methods of catheter placement (Chapter 25) can play an important role in mitigating this risk. In particular, studies have noted that a midline incision through the linea alba, rather than the preferred paramedian approach through the rectus abdominus, is associated with a higher risk for pericatheter leak, as does not using a purse-string suture around the deep cuff embedded in the rectus muscle. Likewise, early use of the catheter, defined as within 2 weeks of insertion, is associated with a higher risk of leak, particularly if larger volumes of dialysate are used.

The general management of pericatheter leaks is conservative. Temporarily holding peritoneal dialysis for a week or more, if possible, allows time for the defect to heal. If necessary, temporary transition to hemodialysis may be necessary, depending on the patient's clinical status. Should the leak persist despite conservative measures, the catheter should be removed and a new catheter inserted at a different surgical site. It may be necessary to discuss the details of the catheter placement procedure with whoever is performing this in order to obviate subsequent leaks.

Should urgent-start peritoneal dialysis be necessary, the risk of pericatheter leak can be reduced by dialyzing the patient in the supine position only, as well as using decreased volumes of dialysate. This strategy allows for appropriate healing of the surgical site by minimizing the increase in intra-abdominal pressure by the dialysis fluid.

Abdominal Wall Leaks

Abdominal wall leaks represent a more significant diagnostic challenge as they generally are less overt than pericatheter leaks, and therefore, their identification may be delayed. These occur when dialysate is able to leak out of a peritoneal membrane defect, usually at the site of catheter insertion, but rather than progress through the catheter tunnel and out the exit site, it instead ends up tracking along a fascial plane in the anterior abdominal wall, resulting in progressive accumulation of dialysate in the abdominal

TABLE 29.1 Risk Factors for Peritoneal Dialysis Leaks

Corticosteroid use
Early (< 2 weeks) start of peritoneal dialysis after catheter insertion
Higher body mass index
Older age
Large dialysate fill volumes
Male gender
Mammalian target of rapamycin (mTor) inhibitor use (e.g., sirolimus)
Method of catheter insertion (midline incision)
Multiparity
Polycystic kidney disease
Previous abdominal surgery

wall. Dialysis fluid can also leak out of the peritoneal cavity through other defects in the peritoneal cavity, such as hernias.

Generally, these patients present after noticing increasing abdominal girth or pressure in absence of significant peripheral edema. Patients may also notice bulging in one area of their abdomen or may also notice a deeper indentation left by their peritoneal dialysis catheter overlying the skin or by the waistband of their pants (Fig. 29.1). Suspicion of an abdominal wall leak should be considered in all patients presenting with poor ultrafiltration with longer dwells, particularly if they are discordant with their peritoneal membrane function determined from their peritoneal equilibration test (PET). Careful clinical exam should be conducted in these scenarios, paying specific attention that the examination is also conducted with the patient standing, as it may help to unmask asymmetry or other differences in the abdominal wall that would be less evident in a standard supine examination.

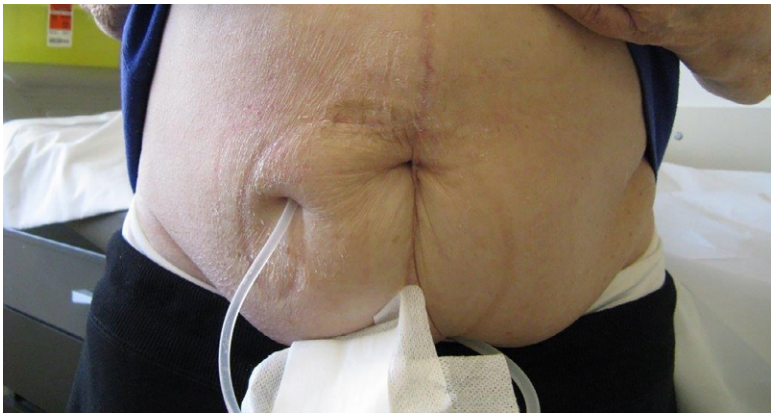
Formal diagnosis of abdominal wall leaks requires either CT peritoneography or technetium-based peritoneal scintigraphy. Either test can be performed by adding the requisite contrast material or radiolabeled tracer to a standard 2L peritoneal dialysis dwell. After instillation of the fluid, the patient should be instructed to be active and walk around for the next 2 hours in order to allow for the fluid to move through the defect and along the tract such that it can be identified during imaging (Fig. 29.2). Failure to allow for sufficient transit time could result in a false-negative test.

Another diagnostic option would be to use magnetic resonance imaging (MRI). In this case, no contrast material is required, as the dialysate itself appears hyperintense (white) on T2-weighted images, allowing it to be easily differentiated from surrounding tissue. The advantage of this technique is that no advance preparation time is required for the test, assuming the patient is already carrying dialysis fluid.

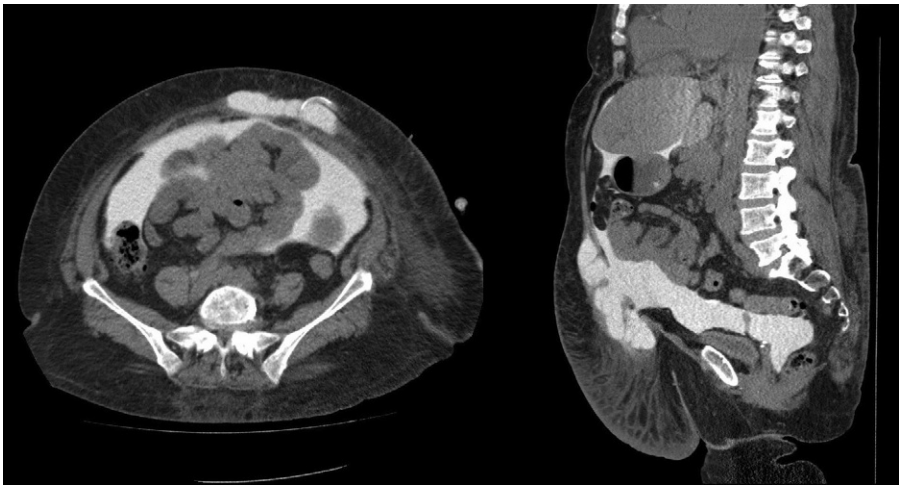
Upon obtaining imaging-based confirmation of an abdominal wall leak, the general treatment would be to change to a nocturnal peritoneal dialysis prescription for 1 to 2 weeks, avoiding a dwell during the day when the patient is ambulatory and subject to higher intra-abdominal pressure. Alternatively, if that is not feasible, then a temporary transition to hemodialysis may be needed. Allowing the patient to have a dry abdomen during the daytime allows for a decreased intra-abdominal pressure and may facilitate healing of the defect. Surgical repair of the defect or catheter removal and replacement can also be considered. In some cases, the patient is able to return to carrying fluid during the daytime; however, others may have recurrent leaks and need either a permanent change to a nocturnal peritoneal dialysis prescription or hemodialysis.

Genital Edema

Similar to abdominal wall leaks, genital edema generally presents more insidiously and takes a longer time to develop. However, this is more likely to be noticed by patients, given the area of involvement, and often due to associated discomfort. Two primary methods exist by which this can



• **Fig. 29.1** Imprinting of the peritoneal dialysis catheter into the abdomen suggestive of underlying abdominal wall leak.



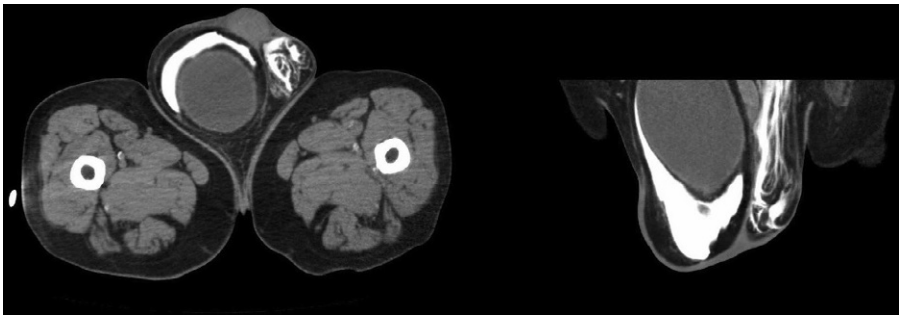
• **Fig. 29.2** Axial and sagittal images of a computed tomography peritoneogram demonstrating an abdominal wall leak.

develop. The first, and less common, is similar to that of abdominal wall leaks, where the defect made by inserting the catheter causes dialysate to leak into the abdominal wall, eventually traveling inferiorly by gravity and resulting in edema of the mons pubis in women and edema of the foreskin and scrotal wall in men. The second, and more common, route is by the fluid directly leaking from the peritoneal cavity into a patent processus vaginalis resulting in a hydrocele. Due to the required descent of the testicles through the processus vaginalis in male development, it is more likely to remain patent, establishing an open conduit between the peritoneal cavity and the scrotal sac. This second pathway generally results in presentations of scrotal edema in men and labial edema in women. The bowel can also traverse a patent processus vaginalis, resulting in an indirect inguinal hernia.

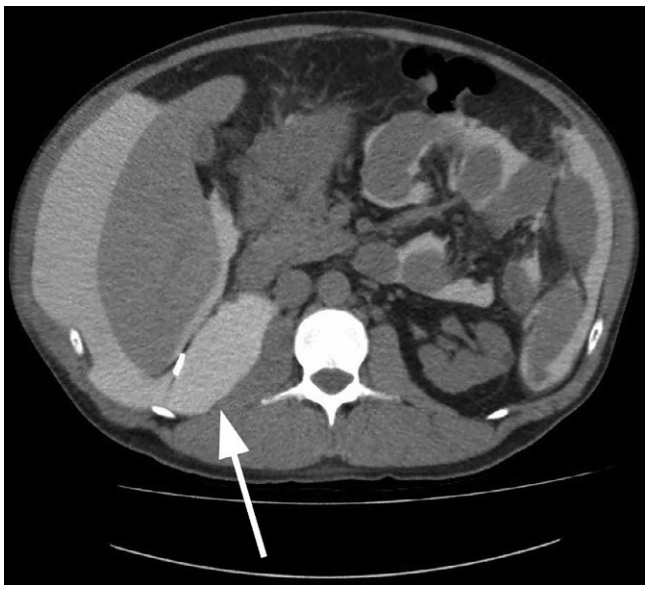
As with abdominal wall leaks, CT peritneography, peritoneal scintigraphy, or MRI can all be used to establish the etiology and pathway of the associated leak (Fig. 29.3). Treatment is also similar to that of abdominal wall leak in that, ideally, peritoneal dialysis is withheld for a short duration, and hemodialysis may become necessary temporarily. Bed rest with elevation of the scrotum can be used for symptomatic relief. If needed, low-volume automated peritoneal dialysis (APD) can be used while the patient remains supine, with a low risk of exacerbating or causing recurrence of symptoms. Surgical correction of the patent processus vaginalis can also be conducted, and upon resumption of peritoneal dialysis, care should be taken to avoid elevated intra-abdominal pressures by using lower volumes and a dry day, if possible, to decrease the recurrence risk.

Retroperitoneal Leaks

Unlike the other causes of dialysate leaks, retroperitoneal leaks are often more difficult to identify and can present a significant challenge to both identify and treat. These leaks most commonly present with patients having exceedingly low or even negative volumes of ultrafiltration despite the use of high-tonicity peritoneal dialysate solutions. Particularly, a sudden change in ultrafiltration without other clinical change in a patient should raise a concern about a potential leak, especially if the reduction in ultrafiltration is greater than 50% of the patient's usual amount. Given the large amount of retroperitoneal space that a leak can accumulate within, there is often no specific physical exam finding that leads to a definitive diagnosis. Patients should be asked about any risk factors related to increased intra-abdominal pressure such as persistent coughing or straining,



• **Fig. 29.3** Axial and coronal images of a computed tomography peritoneogram demonstrating a scrotal leak through a patent processus vaginalis in the left scrotum and an inguinal hernia in the right scrotum.



• **Fig. 29.4** Computed tomography peritoneogram demonstrating a retroperitoneal leak *(arrow)* into the nephrectomy bed following nephrectomy.

use of larger dialysate volumes (2.5L or more), or any recent surgical procedures, as these may precipitate formation of a peritoneal defect.

Initial diagnostic evaluation of such patients should begin with an abdominal x-ray to rule out catheter malposition. Also, a PET is generally the second diagnostic step as the presentation of retroperitoneal leaks is very similar to that of patients who have had changes in their peritoneal membrane characteristics. In such cases, a patient showing any transport status other than high transporter should be concerned about the possibility of a potential leak. Once again, CT peritoneography, peritoneal scintigraphy, or MRI can be used to help identify the source of leak, such as in Fig. 29.4. Upon identification of a retroperitoneal leak, patients should be switched to intermittent peritoneal dialysis with short cycle duration twice weekly for a total duration of 8 weeks, in order to allow for the defect to heal. This is often sufficient in most cases, and reimaging should be performed to ensure that the leak has ceased. Surgical management of these cases is challenging as the exact site of leak may be difficult to pinpoint and may result in other leaks or complications as a result of the procedure.

Summary

Dialysis fluid leakage can present in various different ways. It is crucial to become familiar with the common signs and symptoms that a patient may present with, as in some cases, the diagnosis can be made on clinical presentation alone. If the clinical presentation is not diagnostic, advanced imaging, whether CT peritoneography, peritoneal scintigraphy, or MRI, can be used to evaluate the patient better and determine the underlying diagnosis. In most cases, conservative therapy by either holding PD or limiting the volume or timing of dwells can resolve these problems, but occasionally, more invasive intervention can be necessary. In general, the earlier an issue is diagnosed and treated, the better the likelihood of achieving successful resumption of PD in the long term.

Suggested Reading

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30

Hydrothorax and Peritoneal Dialysis

MOHAMED ELBOKL, MBBCH • JOANNE M. BARGMAN, MD, FRCPC

Introduction

Peritoneal dialysis (PD) hydrothorax is a well-described, albeit uncommon, complication of PD. It results from movement of PD fluid from the peritoneal cavity to the pleural space across the diaphragm. It was first reported in 1967 by Edwards and Unger in a 69-year-old patient who developed acute severe respiratory distress with radiographic evidence of right-sided hydrothorax soon after the commencement of PD.

It is reported in 1.6%–10% of PD patients. Observational studies have documented it to occur almost exclusively on the right side (Fig. 30.1). Several risk factors have been associated with the development of hydrothorax, including female sex, polycystic kidney disease (PKD), previous surgery, and peritonitis.

Pathophysiology

Transudative pleural effusions develop when fluid accumulates in the pleural space in excess of the rate at which it can be reabsorbed. This can happen in the setting of increased plasma hydrostatic pressure, as in congestive heart failure, through decreased oncotic pressure in patients with severe hypoalbuminemia or through fluid entering from the peritoneal cavity, which is what happens in the case of ascites from portal hypertension or PD hydrothorax.

Two factors are involved in the pathogenesis of PD hydrothorax: the presence of a peritoneo-pleural communication and increased intraperitoneal pressure.

Normally, the diaphragm functions as a wall that separates the thoracic and abdominal cavity. Although the normal diaphragm has both large and small openings (stomata) that allow the passage of structures such as the aorta, inferior vena cava, and the esophagus, none of these anatomic stomata allows for transit of intraperitoneal dialysate into the pleural cavity. This is thought to be due to the interface of muscle fibers with serous membranes and other connective tissues.

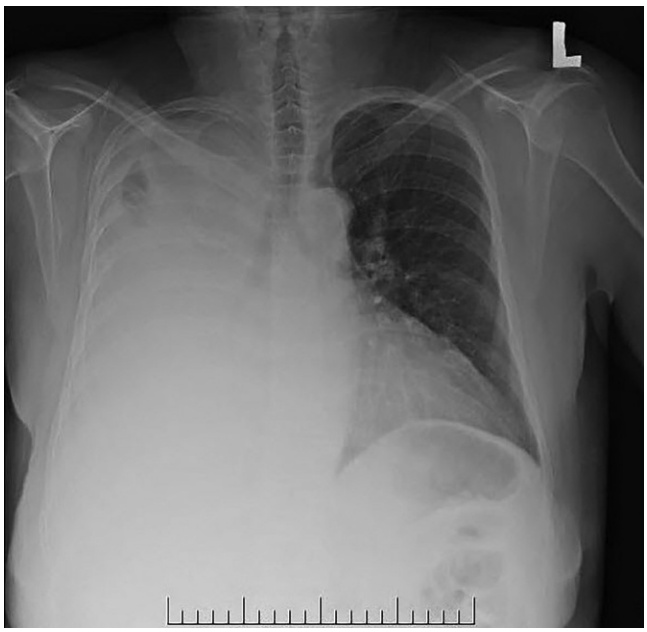
Several mechanisms have been described to explain how fluid could migrate from the peritoneal cavity to the pleural cavity. Gagnon and Daniels proposed that an embryonic remnant, namely, the persisting pneumatoenteric recess and the infracardiac bursa, provides a passage connecting the peritoneal cavity to the right pleural space. It remains unclear why in the majority of patients, the fluid accumulates on the right side of the chest, a phenomenon that is also seen in other conditions such as hepatic hydrothorax, where it has been proposed that pleural effusion is due to increased transport by lymphatics, which are more numerous on the right side. Another potential explanation is the presence of the heart and pericardium in the left hemithorax, which could block some of these diaphragmatic defects and prevent fluid from entering into the left side of the chest.

Increased intraperitoneal pressure can predispose to the passage of PD fluid through acquired diaphragmatic defects. Using large dwell volumes, continuous PD regimens, and/or higher PD fluid tonicity with resultant higher ultrafiltration volumes can precipitate the rise in intraperitoneal pressure. Other activities can contribute to a high intraperitoneal pressure, such as coughing, straining, and exercise.

Symptoms and Presentation

PD-related hydrothorax most commonly presents with shortness of breath, which can be sudden in onset. Physical examination may reveal dullness on percussion and diminished air entry on the side of the effusion, with no other features to suggest volume overload as a cause of the dyspnea, such as peripheral edema. Another clue to the presence of a peritoneo-pleural leak is a persistent decrease in effluent fluid volume, which may be misdiagnosed as an ultrafiltration failure and lead to inappropriate prescription of hypertonic dialysis exchanges, which could increase intraperitoneal volumes and pressure and worsen the hydrothorax.

About 25% of patients with hydrothorax may remain asymptomatic, and the pleural effusion is discovered incidentally. Hydrothorax classically develops shortly after initiation of PD but has been reported to occur as late as 8 years after being on PD. The difference in onset may represent two distinct mechanisms, where early fluid migration happens due to preexisting congenital communications and could happen even with initial small dwell volumes, while later ones occur through acquired defects secondary to a



• **Fig. 30.1** Twenty-six-year-old woman with acute shortness of breath 1 year after starting peritoneal dialysis. Note the massive right pleural effusion.

significant increase in intraperitoneal pressure. In the case of hydrothorax occurring coincident with PD peritonitis, it has been suggested that the inflammation associated with the infection leads to sloughing of a fragile cellular layer overlying a diaphragmatic defect.

Diagnosis

Peritoneo-pleural leak should always be considered when a patient on PD presents with pleural effusion, especially when it happens with the onset of starting PD; however, the usual differential diagnosis of pleural effusion should still apply.

Thoracentesis is of both diagnostic and therapeutic value. Many of these patients present with shortness of breath secondary to the presence of a significant amount of fluid in the pleural cavity, which can be promptly relieved by thoracentesis. In addition, fluid analysis can confirm the diagnosis. The fluid, in this case, should be a sterile transudate, ruling out infectious or malignant etiologies. Although the higher the absolute pleural fluid glucose concentration, the more likely there is communication; there is no cutoff value that can reliably distinguish pleuroperitoneal communication from other causes of hydrothorax. Comparison with a simultaneous plasma glucose has been advocated by some. In a study by Chow et al., a pleural fluid to serum glucose concentration gradient of greater than 50mg/dL was used to differentiate pleuroperitoneal communication from other causes of transudative pleural effusion in PD patients. A glucose gradient has a good positive predictive value but having a gradient less than 50 mg/dL cannot rule out PD hydrothorax. This gradient may be affected by other factors such as the duration and tonicity of the last dwell, fluctuation of serum glucose levels in diabetics, and rate of pleural fluid accumulation. For example, in the case of microscopic or small defects, the accumulation of fluid in the pleural sac could occur slowly, allowing time for systemic glucose absorption from the pleural space into the circulation. If the patient's most recent dwell was icodextrin, a glucose-free dialysis fluid, the pleural fluid glucose concentration would not be expected to be increased; instead, black-blue discoloration may be demonstrated when adding iodine to the drained pleural fluid. In one case report, simultaneous analysis of PD and pleural fluids showed almost identical biochemical profiles.

After an initial chest radiograph, other imaging modalities are usually required to confirm diagnosis of pleuroperitoneal leak; however, most of them lack high sensitivity.

Peritoneal scintigraphy using technetium-99m tagged macro-aggregated albumin or Tc-99m sulfur colloid infused into the PD fluid can confirm pleuroperitoneal communication in a noninvasive fashion by demonstrating radioactive tracer leakage into the thoracic cavity.

Computed tomography (CT) peritoneography can be used to diagnose PD hydrothorax; it has the advantage to possibly detect the site of the leak. Its preparation is similar to that for scintigraphy. In a few case reports, an increase in radiodensity as reflected by difference in Hounsfield units (HU) of the pleural effusion before and after contrast administration could be used to demonstrate the passage of contrast to the pleural space.

Because the rate of movement of dialysis fluid from the peritoneal to the pleural cavity can be slow, ambulation maneuvers to increase intraperitoneal pressure and late images may be needed. Nakayama et al. suggested active straining during time of CT peritoneography to improve imaging sensitivity. Intraperitoneal pressure can increase from 10 cm H_2O at resting to 120–150 cm H_2O during active straining.

Magnetic resonance imaging (MRI) can also be used to diagnose peritoneal defects with similar accuracy to that of CT scans. Previously, gadodiamide, a gadolinium-based contrast, was used in these studies, carrying a risk of development of nephrogenic systemic fibrosis. However, MRIs can be used without the need for additional contrast media administration, where the dialysate, because of its electrolyte content, is used as the contrast medium, which appears bright on T2-weighted images and can therefore detect leaks.

In one case report, PD hydrothorax has been successfully diagnosed by contrast-enhanced ultrasonography using perflubutane, a microbubble contrast agent added to PD fluid and then detected as a high echogenic area on ultrasound images above the level of the diaphragm, indicating peritoneo-pleural communication.

Methylene blue has been added to the dialysis fluid, the fluid instilled in the peritoneal cavity, and then thoracentesis is done to look for blue discoloration of the pleural fluid. However, methylene blue has been reported to cause chemical peritonitis and is, therefore, not recommended. Furthermore, the dye can be overdiluted in the dialysis fluid

and not detectable in the withdrawn pleural fluid, leading to a false-negative result. Indocyanine green has been used in case reports in the same fashion without any reported side effects.

Management

Once PD hydrothorax is suspected, dialysis should be held for 24–48 hours. During this phase, thoracentesis and/or imagining studies should be performed. If the pleural fluid is exudative, another explanation for the effusion should be entertained. In the case of transudative hydrothorax, or where the thoracentesis and imaging studies are not able to confirm PD hydrothorax, PD could be resumed with close observation for possible reaccumulation.

If pleural fluid analysis and imaging studies are highly suggestive of PD hydrothorax, PD should be kept on hold.

Conservative management has been reported to be successful in up to 50% of patients. In this situation, PD is stopped for several weeks to allow time for healing of the defect, and if dialysis is required, patients should be transitioned temporarily to hemodialysis (HD). The patients could be rechallenged with small fill volumes of PD after 4–8 weeks to see if there is recurrence of the hydrothorax. The hypothesis is that the presence of acidic hypertonic PD fluid in the pleural cavity leads to pleural inflammation sufficient to lead to pleurodesis in the healing phase. In our experience, the hydrothorax is likely to recur unless more definitive steps are undertaken.

In some instances where transition to HD would be difficult, hydrothorax is sometimes improved or even eliminated by using a "low-pressure" PD regimen without needing complete stopping of PD during the resting phase. This regimen involves using smaller volumes of PD fluid, intermittent PD, and/or having the patient assume the supine position. There is a general impression that the supine position may allow fluid to move into the pleural cavity more easily, but insofar as it is pressure driven, the supine position would be advantageous in reducing the occurrence of hydrothorax.

Because the diaphragmatic defects become manifest only when there is sufficient intraperitoneal fluid, it should be explained to the patients that if they transition permanently to HD, they will not need any further intervention for the hydrothorax. However, if they want to persevere with PD, pleurodesis or surgical repair will be necessary if the defects do not heal during the resting phase. Because of the high recurrence rate, some authors recommend active intervention at the outset.

Pleurodesis, by instilling a sclerosing agent into the pleural cavity, works by irritating the epithelial surface, leading to inflammation and fibrosis, resulting in obliteration of the trans-diaphragmatic route of dialysate leakage. This procedure can be done blindly through a chest tube or under direct visualization of the pleural cavity using video-assisted thoracoscopy surgery (VATS). The latter has the advantage of being able to evenly distribute the sclerosing agent and potentially achieve better success rates. Different agents have been used in the pleurodesis procedure, including talc and tetracycline, with similar response rates. Autologous blood and bleomycin have also been used, with variable success rates. A 10-day waiting period is the minimum time recommended before PD can be restarted, based on follow-up data using scintigraphy that showed pleuroperitoneal communication healing 10 days after pleurodesis.

In addition to the earlier, VATS has the diagnostic advantage of being able to directly inspect the diaphragm for communications between the pleural and peritoneal cavities. It has better sensitivity than imaging studies. Defects could be blebs, holes, or thinning of the diaphragm. Di Bisceglie and colleagues first described procedure of repair of diaphragmatic defect using VATS in 1996, and it has become the surgical intervention of choice. Prior to that, patients who failed closed pleurodesis had to undergo open thoracotomy, where the diaphragm was visualized and defects directly sutured. Although open thoracotomy carried a high success rate, given the perioperative risks, not all dialysis patients were eligible. Fortunately, this is not a major concern with VATS. Through VATS, different surgical procedures can be done, including surgical repair of the defect by suturing and augmentation muscle flaps, use of fibrin glue and polyglycolic acid sheet, pleurectomy, mechanical abrasion, and chemical pleurodesis. Lastly, VATS allows immediate intraoperative evaluation for air leakage to confirm successful closure of a pleuroperitoneal communication. In the case of microscopic defects in the hemidiaphragm with slow leaks, VATS may not confer any advantage over simple pleurodesis.

The efficacy of thoracoscopic treatment has been confirmed by several case series from various centers, with a more than 90% success rate reported.

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Comprehensive review paper on different management options.

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This case report describes the use of simultaneous biochemical analysis of peritoneal and pleural fluids in the detection of PD hydrothorax.

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This paper describes the use of IP contrast to improve the sensitivity of CT imaging in picking up leaks and other abnormalities.

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Abdominal Catastrophes, Peritoneal Eosinophilia, and Other Unusual Events in Peritoneal Dialysis

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Repeated instillation and drainage of dialysate during the course of peritoneal dialysis (PD) is a unique clinical situation, which infrequently draws attention to primary intra-abdominal events. These events are often unrelated to the PD treatment itself but are brought to attention because of an abnormal appearance of drained dialysate, with or without abdominal pain. They are important for two reasons—first, some conditions such as visceral perforation present with peritonitis. Thus, unless a nephrologist considers the diagnosis of a primary intra-abdominal event, definitive intervention may be delayed. Second, some conditions such as hemoperitoneum are alarming but often require only reassurance of the patient. This chapter discusses several such primary intra-abdominal events.

Abdominal Catastrophe

In patients undergoing PD, the term *abdominal catastrophe* refers to the signs and symptoms associated with either severe visceral inflammation or perforation. This disorder is also called *secondary peritonitis*, *intrinsic peritonitis*, or *peritonitis due to bowel perforation*. Peritonitis secondary to visceral injury is infrequent and is associated with a higher risk of transfer to in-center hemodialysis (HD) or death compared with primary PD-related peritonitis.

Enteric peritoneal contamination may occur as a result of localized inflammation, such as with cholecystitis, diverticulitis, appendicitis, incarcerated hernia, or severe inflammation and/or visceral perforation, as with ischemic colitis or nonocclusive mesenteric ischemia, gangrenous cholecystitis, or perforated gastric or duodenal ulcer. It has been suggested that patients undergoing PD present with abdominal catastrophes more frequently than those undergoing HD or in the general population. However, this data is based on small, single-center studies, and no definitive conclusions can be made in this regard. Rarely, erosion of the Tenckhoff catheter into the ileum or colon may be the primary event leading to visceral perforation; this often is limited to patients with a dormant, indwelling access not being used for PD.

Notwithstanding the early reports, patients with autosomal dominant polycystic kidney disease do not appear to be at a higher risk for either diverticular disease or enteric peritonitis. Furthermore, the relationship of the presence of colonic diverticula to the occurrence of enteric peritonitis or abdominal catastrophe remains unclear. It appears that a large number (≥10) or size (≥10 mm) of diverticuli or a nonsigmoid location may predispose patients to a higher incidence of enteric peritonitis. Yet, most patients with diverticular disease never develop enteric peritonitis or visceral perforation; thus, the presence of diverticulosis should not be considered as a contraindication to PD.

The initial clinical presentation of peritonitis associated with abdominal catastrophes is indistinguishable from PD-associated peritonitis from other causes. An occasional patient will present with abdominal pain with clear dialysate effluent or septic shock. The presence of fecal or biliary material in the effluent, although highly suggestive, is rarely observed. The peritoneal white blood cell (WBC) count is usually higher than with other causes of peritonitis; however, the data are not sufficiently clear to recommend a reliable cut-off value for the peritoneal cell count. Pneumoperitoneum can be present in patients undergoing PD (see later discussion) but does not help in diagnosing visceral perforation. Other imaging studies, such as computed tomography (CT), are often unrevealing as well.

Microbiologically, abdominal catastrophes are associated with a single gram-negative, anaerobic, or fungal organism on the culture; polymicrobial peritonitis is infrequent, and reported to be present in fewer than 20% of patients. Conversely, fewer than 10% of patients with polymicrobial peritonitis have an underlying surgical cause; thus, routine use of laparotomy in patients, with more than one organism on peritoneal fluid culture, is probably inappropriate.

The concentration of amylase in the peritoneal effluent appears to be promising—levels that exceed 500 IU/L seem to be highly suggestive of visceral perforation.

Given this, the diagnosis of abdominal catastrophes in patients undergoing PD is often delayed, and this, in turn, leads to a greater probability of an adverse outcome. Thus, a high index of clinical suspicion is needed to diagnose episodes of peritonitis associated with abdominal catastrophes and should be considered in patients with enteric peritonitis who respond inadequately or incompletely to conventional therapy. Early evaluation by a surgeon is recommended in patients suspected of having an abdominal catastrophe. Large perforations, such as those associated with gastric or duodenal ulcers or ischemic colitis, are often fatal, but smaller, such as those associated with appendicitis or diverticulitis, can be treated with antibiotics alone without need for transfer to in-center HD.

Pneumoperitoneum

In the general population, the presence of air under the diaphragm is considered to be diagnostic of visceral perforation and a trigger for surgical intervention. This remains a potential cause for pneumoperitoneum in patients undergoing PD as well. However, the PD catheter provides an additional port of air entry into the peritoneal cavity; in some patients, the reason for air under the diaphragm on radiography may be related to PD. Pneumoperitoneum may occur after the placement of a PD catheter or manipulation or intervention involving the peritoneal access. Perhaps the most common PD-related cause of pneumoperitoneum is from incomplete priming of the tubing during the instillation of the dialysate that results in the infusion of air into the peritoneal cavity.

Inadvertent introduction of air into the peritoneal cavity may result in patients' presenting with sharp abdominal pain that radiates to the shoulder. However, most cases are diagnosed incidentally, and in an asymptomatic patient with an unremarkable abdominal examination, pneumoperitoneum is generally of little consequence. In a symptomatic patient with significant pneumoperitoneum, rapid relief has been reported with aspiration of air after draining the abdomen of all intraperitoneal dialysate and placing the person in the Trendelenburg position.

In the setting of peritonitis, the presence of pneumoperitoneum has a higher probability of being associated with underlying visceral perforation and requires radiologic workup and, if appropriate, exploratory laparotomy. Contrary to earlier reports, the size of pneumoperitoneum has little predictive value for the diagnosis of visceral perforation.

Iatrogenic Complications of Gastrointestinal or Gynecologic Procedures

There have been several case reports that have documented episodes of peritonitis after sigmoidoscopy or colonoscopy (particularly if accompanied with polypectomy or argon photocoagulation or endoscopic mucosal resection), gastroscopy (particularly if it involves sclerotherapy or heat coagulation), hysteroscopy, endometrial biopsy, or the placement of intrauterine devices. A large case series suggests that peritonitis occurs in <5% of colonoscopies in patients undergoing PD, and observational studies indicate a lower risk in people who receive prophylactic antibiotics. It is unlikely that a randomized controlled trial will be conducted to test the benefit of routine antibiotic prophylaxis when patients treated with PD undergo gastrointestinal (GI) or gynecologic procedures. In light of these considerations, the American Society of Gastrointestinal Endoscopy and the International Society of Peritoneal Dialysis recommend that prophylactic antibiotics that provide coverage against enteric gram-negative and anaerobic bacteria be routinely administered before such procedures in patients treated with PD. It is also recommended that patients drain dialysate from their abdomen before such procedures.

Percutaneous endoscopic gastrostomy (PEG) tubes are used to provide enteral nutrition. The presence of a well-healed PEG tube is not a contraindication to treat a patient with kidney failure with PD. However, the PEG tube and the PD catheter should be clearly marked because inadvertent administration of enteral nutrition feeds into the peritoneal cavity can lead to severe and often fatal chemical peritonitis. On the other hand, placement of a new PEG tube in a patient undergoing PD carries a high risk of infection, particularly fungal peritonitis. Thus, if a patient requires the placement of a PEG tube, PD should be interrupted for 2 to 6 weeks, and the patient should undergo temporary HD.

Pancreatitis

Several population-based studies have suggested that the incidence of pancreatitis may be 30% higher in patients undergoing PD compared with patients undergoing maintenance HD. It is not clear if the higher reported incidence of pancreatitis is from an earlier diagnosis because of the presence of intraperitoneal dialysate or a biological effect of the therapy. It has been proposed that systemic abnormalities, like hypertriglyceridemia, hypercalcemia, or local events, like irritation of the pancreas from the retroperitoneal diffusion of peritoneal dialysate may increase the risk of peritonitis in people treated with PD but remain speculative.

The clinical presentation of acute pancreatitis in patients undergoing PD is often the same as that observed among patients without kidney failure. The peritoneal dialysate is often clear, but it may demonstrate increased total WBC count with or without positive effluent cultures. Hemoperitoneum or chyloperitoneum may be seen occasionally; rarely, the dialysate may be brownish black because of the presence of methemalbumin in patients with hemorrhagic pancreatitis. Although serum amylase levels may be helpful, dialysate amylase (>100 IU/L) provides greater

diagnostic information. However, serum and dialysate amylase are up to sixfold lower among PD patients treated with icodextrin-based dialysate; serum and dialysate lipase levels are more reliable under these circumstances. If radiologic testing is pursued to either diagnose pancreatitis or any of the complications, it is prudent to completely drain all the intraperitoneal dialysate before imaging is performed to provide a better and more complete visualization of the pancreas.

The principles of management of peritonitis in patients with PD are the same as in the general population, and interruption of therapy is not indicated. The data on the prognosis of PD patients with pancreatitis are inconsistent, and population-based studies suggest a similar or slightly higher mortality compared with patients without kidney failure.

Peritoneal Eosinophilia

Among the differential diagnoses of cloudy effluent in patients on PD is peritoneal eosinophilia, a condition with eosinophils constituting greater than 10% of the total peritoneal WBC count and the eosinophil count exceeding 100 cells/mL^3 of peritoneal effluent.

Peritoneal eosinophilia can be seen in the presence of PD-associated peritonitis; however, it can also occur in the absence of peritonitis. In patients with eosinophilic peritonitis, the higher the total WBC count is, the higher is the probability of infectious peritonitis. Conversely, in patients with eosinophils >30% of the total WBC count, the probability of noninfectious etiology is higher. In the past, the leading cause was hypersensitivity to the PD catheter material, possibly the plasticizers or sterilants. Introduction of air or blood into the peritoneum has also been associated with peritoneal fluid eosinophilia. A rare cause is encapsulating peritoneal sclerosis.

Most episodes of peritoneal eosinophilia develop in the first 3 months after initiating PD, with an occasional patient presenting years after starting the therapy. Prior reports put the incidence between 5% and 61%, but the incidence has been significantly lower in recent years, likely because of improvement in the quality of materials used to make PD catheters. Patients typically present with cloudy effluent, and some may have abdominal pain or fever. An elevated blood eosinophil count and elevated immunoglobulin E (IgE) levels are found in some patients. While awaiting cell counts and cultures, it is common to initiate antimicrobial therapy for presumed bacterial peritonitis. With a confirmed diagnosis of noninfective peritoneal eosinophilia, it is appropriate to follow a course of watchful expectancy because most cases resolve spontaneously. Steroids (intraperitoneal or orally) may be used for patients with a protracted course or frequent recurrences. Steroids may also be used in patients with severe abdominal pain or very turbid fluid to maintain catheter patency. Other successful treatment options reported in the literature include antihistamines, ketotifen (a mast cell stabilizer), montelukast, or glycyrrhizin (an extract of licorice with anti-inflammatory properties).

Hemoperitoneum

Hemoperitoneum is not an uncommon complication associated with PD. The presence of even minimal amounts of blood can color the peritoneal fluid pink or red. Performance of the dialysis procedure by PD patients often brings cases to light, which would have been otherwise clinically silent.

The various causes of hemoperitoneum are categorized in Table 31.1. Hemoperitoneum is more common among premenopausal women with causes related to gynecologic conditions, such as retrograde menstruation, ovulation, cyst rupture, and endometriosis. Hemoperitoneum with

TABLE 31.1 Causes of Hemoperitoneum

Gynecologic Disorders
Ovulation (midcycle)
Retrograde menstruation (with periods)
Ruptured ovarian cyst
Endometriosis (with periods)
Ectopic pregnancy
Associated with Acute Abdomen
Acute hemorrhagic pancreatitis
Acute cholecystitis
Splenic rupture or infarction
Peritonitis
Peritoneal Membrane Abnormalities
Encapsulating peritoneal sclerosis
Peritoneal carcinomatosis
Peritoneal calcification
Radiation injury
Miscellaneous
Trauma
Exercise
Postprocedures such as colonoscopy, pericardiocentesis, or cardiopulmonary resuscitation
Bleeding disorders
Rupture of hepatic or kidney cysts
Kidney or liver tumors
Retroperitoneal hematoma
IgA nephropathy
Idiopathic

retrograde menstruation or endometriosis usually presents before the onset of vaginal bleeding. These patients are most likely to have recurrent hemoperitoneum. In a number of patients, no definite etiology can be determined; it has been suggested that hemoperitoneum may have been a result of minor tears of the omental vessels. Occasionally, the peritoneal catheter has been reported to erode into the major mesenteric vessels, leading to hemoperitoneum.

Most cases of hemoperitoneum are benign. Uncommonly, hemoperitoneum is a sign of underlying intraperitoneal pathology; in these patients, bleeding often persists beyond 36 hours. Major hemorrhage is uncommon, and it is highly unusual for patients to require blood transfusions or surgical intervention. An initial assessment includes a thorough history, including details of menstruation, recent trauma, and use of anticoagulant or antiplatelet drugs. The patient should undergo an assessment of the hemodynamic status and be examined for signs of an abdominal catastrophe. Subsequent evaluation is often dictated by this initial assessment.

The management of hemoperitoneum is often expectant and, if necessary, directed at the primary cause. The first step is peritoneal lavage two or three times—if the subsequent effluent clears, it suggests that the intraperitoneal bleeding was self-limited, and no further intervention is needed. If the effluent does not clear, it is prudent to add 500–1000 units of heparin to each bag of dialysate up until the hemoperitoneum persists to prevent occlusion of the PD catheter. Instillation of unwarmed dialysate at room temperature has also been proposed to induce vasoconstriction of the peritoneal circulation by the cooler dialysate to slow the bleeding. However, care should be exercised to avoid hypothermia during the winter months in cold locales. Desmopressin and unconjugated estrogens can ameliorate uremic bleeding.

Chyloperitoneum

Chyloperitoneum results from the leakage of chyle into the peritoneal cavity. Patients present with turbid or typical milky dialysate. The diagnosis is confirmed if chylomicrons are detected or dialysate triglyceride levels are higher than the plasma level. Patients undergoing PD can lose substantial amounts of protein and lymphocytes with repeated exchanges leading to protein-energy wasting and immunosuppression. Excessive fluid loss causing dehydration can also be an issue.

The underlying causes are related to either interruption or obstruction of the lymphatic system. Malignancies, especially lymphomas, are reported as the most common cause of chyloperitoneum. Trauma, either at the time of insertion of the peritoneal catheter or from repeated catheter movement, acute and chronic pancreatitis, cirrhosis, amyloidosis, superior vena cava syndrome, and tuberculous peritonitis are other causes of chyloperitoneum. Elevations of peritoneal triglycerides have also been associated with the use of dihydropyridine calcium channel blockers such as lercanidipine and manidipine.

Evaluation of patients should include a detailed history and physical examination along with CT scans, MRI, or lymphoscintigraphy, as indicated. In some settings, chyloperitoneum is transient and/or resolves after discontinuation of a drug or treatment of an underlying condition, such as tuberculosis. Strategies on the treatment of persistent chyloperitoneum focus on decreasing production of chyle and treatment of the underlying cause. Long-chain fatty acids are absorbed from the bowel directly into the lymphatic system and contribute to chyle flow; medium-chain triglycerides are absorbed directly into the bloodstream and decrease chyle flow. Thus, high-protein, low-fat diets containing medium-chain triglycerides can be used and over several months have been shown to be effective. Bowel rest with total parenteral nutrition is an alternative. Octreotide, a somatostatin analog, has been reported to be effective in anecdotal reports.

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32

Metabolic Complications of Peritoneal Dialysis

RAJNISH MEHROTRA, MD, MS

The removal of solute and water for the management of kidney failure with peritoneal dialysis (PD) is achieved by exposing the naturally occurring peritoneal lining of the abdomen to 6 to 15 L of dialysate every day. It is widely believed that the exposure of the peritoneum to large volumes of dialysate has significant and wide-ranging deleterious systemic effects. This chapter reviews the evidence for and the clinical implications for the purported systemic metabolic effects of PD.

Weight Gain

Every patient treated with PD uses glucose-based solutions either exclusively or for most of the treatment through the day, with the remaining time with either icodextrin- or amino acid-based solutions. Treatment with glucose- or icodextrin-based solutions is associated with an obligatory absorption of 50 to 150 g of carbohydrates daily. As a result, it is widely believed that patients treated with PD are significantly more likely to gain body weight than those undergoing hemodialysis (HD). At times, this may be an important consideration in the selection of dialysis modality for some patients because of either the effects on body image or future eligibility for transplantation.

Caution must be exercised in interpreting data on changes in body weight over time because they may result from alterations in volume status, fat mass, or fat-free edema-free body mass. Initiation of dialysis is associated with two competing events—improvement in volume status by correction of hypervolemia with dialysis as well as an improvement in appetite from the amelioration of anorexia, a cardinal manifestation of the uremic state. This results in a net decrease in body weight in the first few months of initiation of dialysis followed by weight gain in most patients irrespective of dialysis modality. Three large multicenter studies have compared the change in body weight after initiation of dialysis and demonstrated either no significant difference in the trajectory of change in body weight over time for patients treated with HD, PD, or a higher probability of significant weight gain for patients treated with HD. Hence, the notion that patients are more likely to gain significant body weight with PD is not supported by the available evidence. Limited evidence suggests that the magnitude of weight gain with PD may at least in part be determined genetically. Small single-center studies also seem to indicate that patients treated with PD may be more likely to gain visceral fat mass than those undergoing HD. These findings need to be validated in larger studies, but their clinical implications are unclear.

Thus, after the first few months of treatment with maintenance dialysis, patients gain body weight irrespective of modality, and concerns about a higher probability of weight gain with PD are not supported by the available evidence. It follows then that concerns about weight gain should not be an important consideration in the selection of dialysis modality.

Metabolic Syndrome

Metabolic syndrome is defined as the presence of a cluster of risk factors that are associated with a significantly higher risk for cardiovascular disease in the general population. The definitions for metabolic syndrome from different expert groups are somewhat different but generally include measures of adiposity, dyslipidemia, hypertension, and abnormal fasting blood glucose levels. Insulin resistance is the dominant but not the only condition underlying the pathogenesis of metabolic syndrome. The different components of the metabolic syndrome are independent risk factors for the development and progression of chronic kidney disease (CKD); hence, patients with metabolic syndrome are significantly more likely to have CKD. Conversely, metabolic syndrome is highly prevalent in patients with kidney failure, including those undergoing maintenance dialysis.

Several studies have demonstrated that half or more of patients undergoing PD meet the criteria for metabolic syndrome by one or more expert groups. However, there is only a fair to modest agreement in the diagnosis of metabolic

syndrome using the various criteria. A small longitudinal cohort study has demonstrated an increase in the prevalence of metabolic syndrome over time when treated with PD, and another study that made a head-to-head comparison concluded that metabolic syndrome was significantly more prevalent in patients undergoing PD compared with in-center HD. These observations have raised concerns that PD therapy may contribute to the development of metabolic syndrome. This is thought to be biologically plausible given the obligatory carbohydrate absorption with PD. However, the data are preliminary at best for several reasons. The prevalence of metabolic syndrome for patients undergoing in-center HD in the only study with head-to-head comparison was substantially lower than in other studies. Also, there are at least two challenges with the diagnosis of metabolic syndrome in patients undergoing PD. First, the intraperitoneal instillation of dialysate with PD results in an increase in waist circumference, an important component for the diagnosis of metabolic syndrome. Second, there is continuous systemic absorption of glucose from intraperitoneal dialysate, and hence, patients undergoing PD are never in a postabsorptive state. This results in an overestimation of fasting glucose and lipid parameters. These challenges likely also explain, in part, the variability in who is diagnosed (or not) with metabolic syndrome based upon the expert group criteria used. Finally, the results from studies examining the association of metabolic syndrome with cardiovascular events or all-cause mortality have been inconsistent and may depend upon the diagnostic criteria used. This is not surprising because the individual components of metabolic syndrome themselves do not portend a higher risk for death or cardiovascular events in patients with kidney failure, including those undergoing PD.

For these reasons, the contribution of PD to the development of metabolic syndrome and its clinical relevance for these patients is at best uncertain. Notwithstanding these uncertainties, it remains prudent to minimize daily glucose exposure with PD prescription.

New-Onset Diabetes Mellitus in Nondiabetic Patients

New-onset diabetes mellitus is more common in people with kidney failure undergoing treatment with long-term dialysis than in the general population. There are several possible reasons for the occurrence of new-onset diabetes mellitus, including an increase in insulin resistance over time with loss of residual kidney function or weight gain with amelioration of uremic anorexia. It is also possible that some patients may have had previously undiagnosed diabetes mellitus that becomes apparent with improvement in the uremic state or increase in dietary intake with initiation of dialysis. Concern has been raised that systemic glucose absorption with PD may also contribute to new-onset diabetes mellitus, but as discussed earlier, caution must be exercised in interpreting fasting blood glucose concentrations given the continuous systemic carbohydrate absorption with PD. To determine the contribution of PD therapy to the occurrence of new-onset diabetes mellitus, several studies have made head-to-head comparison in the incidence of the condition in patients treated with PD and HD with inconsistent findings (ranging from lower risk with PD to no difference to higher risk with PD). Two meta-analyses of these data show no difference in the risk for new-onset diabetes mellitus in people treated with PD or HD. Hence, there is no consistent evidence to support the notion of a higher risk for new-onset diabetes mellitus in patients undergoing PD. Nevertheless, the condition is common enough that nondiabetic patients undergoing maintenance dialysis should have a periodic measurement of blood glucose with further workups, such as with the measurement of glycosylated hemoglobin, as appropriate.

Hyperglycemia in Patients With Diabetes Mellitus

In patients with diabetes mellitus, initiation of PD is associated with worsening glycemic control because of both increased dietary intake and obligatory systemic carbohydrate absorption with the therapy. The magnitude of increase in blood glucose levels is associated with the concentration of glucose in the dialysate. Given these observations, it is imperative that patients with diabetes mellitus monitor home blood glucose levels closely in the first few months of initiation of PD. Furthermore, most patients with diabetes treated with PD require an escalation of glucose-lowering therapy or need to initiate treatment for diabetes mellitus in patients who had previously been diet controlled.

It is important to take into account the PD prescription when adjusting glucose-lowering therapy. As discussed earlier, patients undergoing PD are invariably absorbing glucose through the 24-hour period, and in patients undergoing automated PD, a substantial proportion of this absorption occurs overnight, when most other patients are in the postabsorptive state. It is also important to adjust glucose-lowering therapy when patients adjust the tonicity of the dialysate. In that context, at least two multicenter clinical trials have demonstrated that glucose-sparing PD regimens that variably use icodextrin and/or amino acid solutions throughout the day are associated with an improvement in glycemic control.

There have been significant advances in the management of patients with diabetes generally, with a greater use for more intensive monitoring of blood glucose, such as with continuous glucose monitoring and with the introduction of new classes of drugs, for example, sodium-glucose-transport protein 2 (SGLT2) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors. It is likely that a growing number of patients treated with PD may be managed with continuous glucose monitoring as well, but there is presently no meaningful evidence to determine treatment goals. The Food and

Drug Administration has approved the use of many GLP-1 receptor agonists and DPP-4 inhibitors in people with kidney failure, and an increasing number of patients treated with PD are likely to be treated with these drug classes, in addition to conventional therapies (insulin, sulphonylureas, and thiazolidinediones). SGLT2 inhibitors, a drug class with the greatest benefit in slowing the decline of kidney function and reducing cardiovascular risk, are currently contraindicated for use in patients with advanced kidney failure.

The data on health benefits of improved glycemic control in patients undergoing PD is substantially limited. Like in the general population, improved glycemic control should be expected to prevent or slow the progression of microvascular disease (e.g., retinopathy or neuropathy). However, there are no data to date for patients undergoing PD. Furthermore, it is not clear if improved glycemic control would reduce the progression of macrovascular disease or lower all-cause mortality. As for the general population, observational studies have demonstrated an association between measures of glycemic control (blood glucose, glycosylated hemoglobin, or glycated albumin) and risk for death in patients undergoing PD. In contrast, none of the clinical trials to date has been able to demonstrate a reduction in risk for death with improvement in glycemic control in patients with diabetes mellitus in the 3 to 5 years span of life expectancy of patients with PD. The cardiovascular risk reductions seen with new drug classes such as SGLT2 inhibitors and GLP-1 receptor agonists are thought to be class-specific effects, independent of their glucose-lowering effects. It would be unreasonable to expect a reduction in cardiovascular risk or increased life expectancy with aggressive glycemic control in individuals with diabetes mellitus undergoing PD. Given this uncertainty and the potential risks with hypoglycemia, it is currently not possible to recommend a target range for various indices for glycemic control in patients undergoing PD.

Lipid Abnormalities

It is often said that patients undergoing PD have a more atherogenic lipid profile than patients undergoing HD and, by extension, that the PD therapy itself contributes to the dyslipidemia. Lipid abnormalities in patients undergoing PD have been attributed to obligatory glucose absorption and peritoneal protein loss with consequent hypoalbuminemia as with patients with nephrotic syndrome. Although conceivable, there are few head-to-head comparisons of lipid profiles of patients treated with different dialysis modalities that preclude a definitive conclusion about the relative prevalence of dyslipidemia and contribution of PD to the same. Moreover, as discussed earlier, patients undergoing PD are never in the postabsorptive state, so lipid parameters in these patients cannot be considered to be "fasting" values. There is also preliminary evidence that dialysis modalities may affect the composition and functionality of lipid moieties such as high-density lipoprotein differently. The clinical implications of these differential changes in lipid moieties, if any, remain unknown.

Statin drug therapy remains the mainstay for the management of hyperlipidemia in patients undergoing PD and is safe and similarly effective as in the general population. Clinical trials have demonstrated that substituting glucose-based dialysate in one or more exchanges with icodextrin- and/or amino acid-based solutions are associated with a modest reduction in total or low-density cholesterol or triglycerides. However, the magnitude of reduction and the lipid parameters that improve have been inconsistent among studies. Nevertheless, adjusting the PD prescription is a reasonable approach for patients for whom drug therapy is not effective in achieving the desired goal or who develop unacceptable adverse effects of treatment.

There are limited clinical trial data on the health benefits of lipid lowering in patients undergoing PD. The Study of Heart and Renal Protection (SHARP) enrolled a large population of patients treated with PD, and many more patient-initiated treatment with PD during the course of the trial. The clinical trial demonstrated that treatment with simvastatin-ezetimibe was associated with a significant reduction in risk for cardiovascular events, and there was no effect modification with dialysis status. Put differently, the same nature and magnitude of benefit could be expected for patients undergoing maintenance dialysis as observed in the study at large. Yet, there was no significant reduction in all-cause or cardiovascular mortality with such treatment. Hence, the magnitude of the health benefit with lipid lowering in patients with kidney disease, including those undergoing PD, is significantly lower than in the general population.

Hypokalemia

Unlike virtually any other population of patients with kidney disease, hypokalemia is common in patients undergoing PD. There are likely several factors contributing to the high prevalence of hypokalemia, including dialysate potassium loss, particularly in the face of low dietary intake, transcellular shift induced by endogenous insulin release in response to systemic glucose absorption, kidney losses with use of diuretics, or intestinal losses with use of laxatives. Observational studies have also demonstrated a consistent association of low serum potassium levels with a higher risk for gram-negative peritonitis and all-cause, cardiovascular, and infection-related mortality.

Not only are there no clinical trials that have demonstrated the health benefits of treatment of hypokalemia in patients undergoing PD, but none is likely to be done in the near future. Given the frequency of occurrence for hypokalemia and the associated health risks, it is important to routinely monitor and correct serum potassium levels in patients undergoing PD. As a first step, dietary restrictions on potassium intake should be removed and the intake liberalized. In patients with persistent hypokalemia,

inhibitors of the renin-angiotensin-aldosterone axis should be considered (e.g., angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or spironolactone). Most patients, however, are likely to require oral potassium supplements.

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SECTION 4

Management of Uremic Complications

33

Acid–Base Homeostasis in Dialysis

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When renal replacement therapy is initiated, regulation of acid-base balance by the kidneys is replaced by a new homeostatic process responding to the physical principles of diffusion and convection rather than to the pH of the body fluids. Consequently, blood HCO_3^- concentration ($[HCO_3^-]$) in the steady state is dependent in large part on the kinetics of HCO_3^- diffusion across the dialysis membrane. Despite the lack of a pH-dependent regulatory system, a new equilibrium is achieved during dialysis therapy in which HCO_3^- consumption by endogenous acid production (including any alkali lost in the stool) in the interval between treatments is matched by HCO_3^- addition during dialysis. During conventional hemodialysis, but not peritoneal dialysis, a surge in organic acid production occurs during treatment in response to rapid alkalinization, the magnitude of which is another determinant of the predialysis blood $[HCO_3^-]$ at which this equilibrium occurs.

Although dialysis therapy creates a new equilibrium, it is much less able adapt to day-to-day changes in acid production or to superimposed disorders of acid-base equilibrium. This chapter reviews the nature of this unique regulatory process and the tools for identifying disturbances of acid-base homeostasis in dialysis-dependent patients. Throughout the chapter, the term *[total CO_2]* refers to the routinely measured variable in serum that correlates closely with blood $[HCO_3^-]$, and the term *$[HCO_3^-]$* refers to the value calculated from measurements of P_{CO_2} and pH in blood or to the concentration of bicarbonate in the dialysate solution.

Determinants of Blood $[HCO_3^-]$ in Dialysis Patients

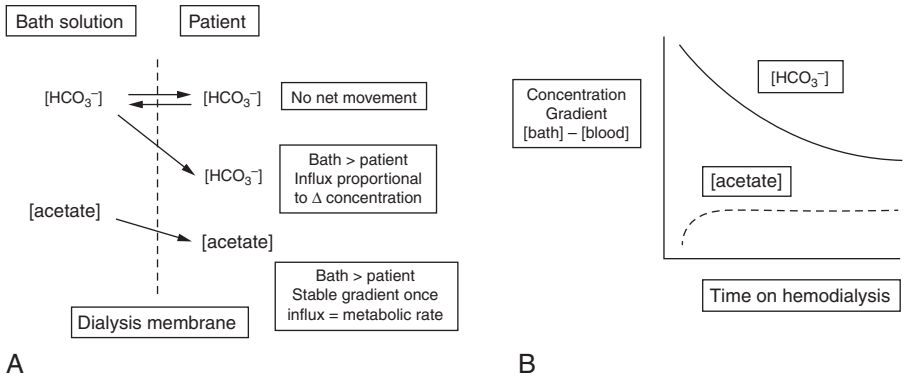
The amount of HCO_3^- added during both hemodialysis and peritoneal dialysis is related to the dialysance of the alkali source used (HCO_3^- and acetate or citrate in hemodialysis; lactate or HCO_3^- in peritoneal dialysis) and to the transmembrane concentration gradient. With hemodialysis, dialysance is a function of the permeability and surface area of the specific dialysis membrane used. With peritoneal dialysis, dialysance is a function of the permeability and surface area of the patient's peritoneal membrane.

Fig. 33.1 illustrates the forces driving alkali addition and the time course of the transmembrane concentration gradients for the ions of interest in hemodialysis. Fig. 33.2 illustrates the same features for peritoneal dialysis. With the exception of blood $[HCO_3^-]$, these parameters are set by the dialysis prescription. As a result, blood $[HCO_3^-]$ is the variable that determines the total amount of HCO_3^- added and retained during treatment. The lower the blood $[HCO_3^-]$ at the onset of hemodialysis, the greater the HCO_3^- influx. The lower the blood $[HCO_3^-]$ at the initiation of peritoneal dialysis, the more HCO_3^- is retained during treatment. With both types of dialysis therapy, therefore, a new equilibrium is achieved in which the alkali consumed in buffering endogenous acid production (a process that reduces blood $[HCO_3^-]$) is approximately matched by the HCO_3^- added and retained during treatment.

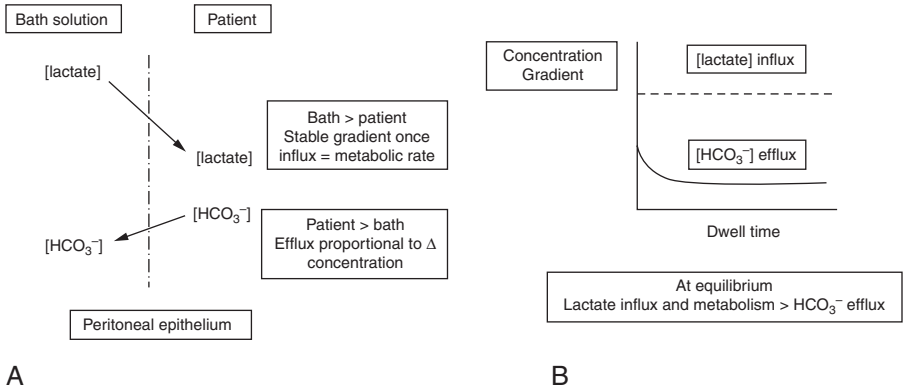
Hemodialysis

Hemodialysis bath solutions around the world contain widely varying bath $[HCO_3^-]$ values, from as low as 25 mEq/L in Japan to as high as 40 mEq/L in some patients in the United States. This variability reflects the lack of studies defining the optimal bath concentration for achieving a normal predialysis blood $[HCO_3^-]$ and pH. The wide range of bath values tolerated is likely due to parallel variations in buffering and/or organic acid production, a homeostatic response that minimizes the change in pH that occurs during the dialysis session. Most commonly, bath solutions contain $[HCO_3^-]$ values of 32–35 mEq/L.

In addition to HCO_3^-, hemodialysis bath solutions contain an organic anion, either acetate or citrate, in low concentration. These anions are produced by the reaction of their respective organic acids with HCO_3^- during the generation of the final bath solution, a chemical event necessary to keep bath pH in a range that prevents precipitation of calcium and magnesium salts. Generation of HCO_3^- from these organic anions is determined by their rate of influx and metabolism. In contrast to HCO_3^-, the transmembrane gradient for these organic anions remains constant during dialysis once influx rate equals metabolic rate (Fig 33.1B), and therefore, these anions are the source for as much of



• **Fig. 33.1** Schematic Representation of Transmembrane HCO_3^- and Acetate Movement During Hemodialysis. (A) Effect of the transmembrane gradient on ion movement. (B) Diagram of the time course and magnitude of the transmembrane concentration gradient (without units) for these ions during hemodialysis. For HCO_3^-, Δ concentration falls rapidly during the first hour of dialysis but rarely reaches equilibrium with the bath. By contrast, Δ concentration for acetate rises rapidly until influx = metabolism, after which it remains stable for the duration of treatment.



• **Fig. 33.2** Schematic Representation of Transmembrane HCO_3^- and Lactate Movement During Peritoneal Dialysis. (A) Effect of the transmembrane gradient on HCO_3^- and lactate movement. These ions move in opposite directions throughout the dialysis bath dwell period. (B) Time course (without units) of the concentration gradients. Lactate influx rate is constant throughout the dwell period as lactate metabolism matches influx almost instantaneously. Because the bath contains no HCO_3^-, there is an initial surge in HCO_3^- efflux from the patient that is proportional to Δ concentration. Within 15 minutes, bath $[HCO_3^-]$ rises to ~80% of extracellular fluid $[HCO_3^-]$ and efflux continues but at a much lower rate.

35%–50% of the total HCO_3^- added during treatment, despite their low bath concentration.

In patients receiving intermittent hemodialysis, predialysis serum [total CO_2], the parameter usually measured, is determined by the dialysis prescription and patient characteristics outlined in Table 33.1. Of the patient characteristics, the first two, endogenous acid production and fluid retention between treatments, are the primary determinants of predialysis serum [total CO_2]. Renal generation and loss of HCO_3^- are usually trivial. Organic acid production during dialysis has a notable impact on the net addition of alkali during dialysis but is a stable feature of the bath $[HCO_3^-]$ prescribed, and therefore, it has little effect independent of the dialysis prescription unless it is unusually large (see discussion of metabolic acidosis later in the chapter). The estimated effects of variations in endogenous acid production and fluid retention between treatments are shown in Table 33.2.

As shown in the table, variations in endogenous acid production over a reasonable range can change predialysis serum [total CO_2] from normal to frankly acidotic values. Endogenous acid production varies directly with dietary intake of sulfur-containing proteins. Thus, patients with limited intake of animal protein and grains will have a higher predialysis serum [total CO_2] than patients eating a diet high in these foods. Variations in fluid retention have a smaller but clinically significant effect.

Hemodialysis three times weekly does not restore predialysis serum [total CO_2] to 24 mEq/L unless endogenous acid production is low. Before 2005, the average predialysis value ranged from 19 to 23 mEq/L in stable outpatients, but more recently, the range has risen to 23–26 mEq/L, suggesting that endogenous acid production has fallen. The cause is unknown but seems likely to be due to a difference in diet, reflecting an older and more debilitated hemodialysis population. It is important to emphasize that predialysis

TABLE 33.1 Determinants of Predialysis or Steady-State Serum [Total CO_2] in Patients Receiving Dialysis Therapy

Hemodialysis prescription

- Bath [HCO_3^-]
- Bath [acetate], [citrate] or [lactate] (used in some types of daily dialysis)
- Permeability and surface area of dialysis membrane
- Blood and dialysate flow rates
- Duration and frequency of dialysis treatments

Peritoneal dialysis prescription

- Bath [lactate] (or [HCO_3^-] used in some cases)
- Volume and dwell time of exchanges
- Permeability and surface area of peritoneal membrane

Patient characteristics

- Endogenous acid production
- Fluid retention*
- Renal HCO_3^- generation or loss in patients with residual renal function
- Organic acid production during dialysis treatments†

* Fluid retention affects the space of distribution and, therefore, the extracellular fluid [HCO_3^-].
† Hemodialysis only.

TABLE 33.2 Estimated Effect of Endogenous Acid Production and Fluid Retention on Predialysis Serum [Total CO_2] in Patients Receiving Hemodialysis With a Bath [HCO_3^-] = 35 mEq/L

Endogenous Acid Production, mEq/day*	Predialysis Serum [Total CO_2], mEq/L†
30	24.2
60	21.9
90	19.6
120	17.3
Fluid Retention (L)‡	
0	23.1
2	21.9
4	20.8
6	19.8

Other assumptions: weight 70 kg, postdialysis serum [total CO_2] = 28 mEq/L, HCO_3^- buffer space = 0.5 × body weight.
* Assuming 2 L fluid retention between treatments.
† After a long interval between treatments (68 hours).
‡ Total fluid gain between treatments, assuming 60 mEq/day endogenous acid production.

[total CO_2] is a nadir value. Serum [total CO_2] rises to 28–32 mEq/L just after each hemodialysis treatment and gradually falls to the predialysis level over the interval between treatments. Not surprisingly, the lowest predialysis value occurs after the longest interval (68 hours) between treatments. At the end of the shorter interval (44 hours), the value is approximately 1 mEq/L higher.

Two large cohort studies have demonstrated an increased mortality risk both in patients with low (< 19 mEq/L) and high (> 26 mEq/L) predialysis serum [total CO_2] values. In the former group, the increased risk appears to be directly attributable to the presence of metabolic acidosis. In the latter group, the increased risk is associated with alkalosis but appears to be primarily caused by negative nutritional and inflammatory factors. Predialysis serum [total CO_2] can be varied by adjusting bath [HCO_3^-], and short-term studies have shown that in patients with low values (< 20 mEq/L), raising the value sufficiently to increase serum [total CO_2] to 24 mEq/L has beneficial effects on both muscle and bone metabolism. Although this practice has been widely adopted in the United States, a more recent large cohort study suggests that increasing bath [HCO_3^-] is an independent risk factor for death, raising the likelihood by 8% for every 4 mEq/L increase. Increasing bath [HCO_3^-] appears to increase the buffering and metabolic response to rapid alkali addition during treatment, and the latter is a potentially maladaptive response.

Peritoneal Dialysis

Peritoneal dialysis is a continuous therapy and is therefore much less disruptive from an acid-base perspective. With this form of renal replacement therapy, steady-state serum [total CO_2] is also determined by the dialysis and patient characteristics outlined in Table 33.1. The dynamic features of alkali addition during dialysis are illustrated schematically in Fig. 33.2. Panel A in the figure highlights the fact that lactate diffuses from the bath into the patient and HCO_3^- diffuses from the patient to the bath during dialysis. Panel B shows that the time course of the transmembrane concentration gradients differs notably from hemodialysis. The gradient for lactate influx basically remains constant throughout the bath dwell period. A large gradient is maintained by rapid metabolism of the added lactate ions, generating new HCO_3^-. Blood [lactate] does not rise notably during dialysis. Immediately after instilling a fresh bath, there is a rapid efflux of HCO_3^- from patient to the bath, as it contains no HCO_3^-. The magnitude of this initial loss is inversely related to the extracellular fluid (ECF) [HCO_3^-]. Within 15 minutes, bath [HCO_3^-] rises to ~ 80% of the ECF concentration, and efflux continues but at a much slower rate. At the end of the dwell, net influx of lactate exceeds HCO_3^- efflux, so that ~ 50 mEq of HCO_3^- is added to the patient each day with four 6-hour dwell periods.

Bath [lactate] has empirically been set to maintain a serum [total CO_2] in the normal range in most patients,

at 40 mEq/L. In some centers in Europe, peritoneal dialysis with an HCO_3^--containing bath solution (mixed just before instillation) has improved acid-base status further, but this technique is technically cumbersome and has not gained wide acceptance. The higher exchange volumes and shorter dwell times now routinely used in continuous cycling peritoneal dialysis do not change serum [total CO_2] notably.

Normal Values

The ranges of "normal" values for predialysis serum [total CO_2] and for blood pH, P_{CO_2}, and [HCO_3^-] in patients receiving conventional hemodialysis, and the steady-state values for these parameters in patients receiving peritoneal dialysis are shown in Table 33.3. In patients receiving hemodialysis, average serum [total CO_2] has risen by 1–2 mEq/L in the last decade without any change in dialysis prescription, possibly reflecting a lower protein intake in the older population now receiving this treatment. Blood P_{CO_2} and pH measurements indicate either an essentially normal acid-base status or a mild acidosis with an appropriate secondary respiratory response. Patients receiving peritoneal dialysis have average values for venous serum [total CO_2] in the normal range, although limited arterial acid-base measurements in these patients also show a very mild acidosis.

TABLE 33.3 Steady-State Acid-Base Values in Stable Dialysis Patients

	Conventional Hemodialysis	Peritoneal Dialysis
[total CO_2] mEq/L	23.9 ± 2.1 (175)*	26.4 ± 3.0 (109)†
[HCO_3^-] mEq/L	21.3 ± 2.5 (14)‡	21.5 ± 2.4 (33)§
pH	7.38 ± 0.05 (14)	7.38 ± 0.04 (33)
P_{CO_2} mm Hg	36 ± 3.1 (14)	37 ± 5.1 (33)

* Measured in 2016 in graft or fistula blood samples, pre-dialysis after long interval in stable outpatients. Hemodialysis bath [HCO_3^-] = 35 mEq/L, bath [acetate] = 4 mEq/L. Gennari FJ, personal observation.
† Venous blood measurements. Data from Gennari FJ, Feriani M. Acid base problems in hemodialysis and peritoneal dialysis. In: Lameire N, Mehta RL, eds. *Complications of Dialysis*. New York: Marcel Dekker; 2000:361–376.
‡ Blood [HCO_3^-], pH, and P_{CO_2} values in hemodialysis patients obtained predialysis from arterial blood, 2008–2012. Hemodialysis bath [HCO_3^-] = 32 mEq/L, bath [acetate] = 3 mEq/L. Data from Sargent JA, Marano S, Marano M, Gennari FJ. Acid–base homeostasis during hemodialysis: new insights into the mystery of bicarbonate disappearance during treatment. *Semin Dial.* 2018;31:468–478.
§ [HCO_3^-], pH, and P_{CO_2} values in peritoneal dialysis patients obtained from arterial blood. Peritoneal bath [lactate] = 40 mM. Data from Feriani M. Use of different buffers in peritoneal dialysis. *Semin Dial.* 2000;13:256–260.
Data are means ± SD, numbers in parentheses are the numbers of patients.

Diagnosis and Management of Acid-Base Disorders

The nephrologist caring for patients receiving dialysis therapy has two tasks with regard to their acid-base status. The first is to identify patients with either persistently low values for serum [total CO_2] (less than 20 mEq/L) or persistently high values for serum [total CO_2] (greater than 25 mEq/L) and to determine whether treatment modification can improve this situation. The second task is to uncover superimposed acute acid-base disturbances. In making either assessment, serum samples for total CO_2 must be processed and run in a timely fashion. Shipment of blood samples to a distant laboratory and delay in analysis may spuriously reduce the value by as much as 5 mEq/L. If a low or high serum [total CO_2] is validated, the next step is to obtain an arterial blood sample for measurement of pH and P_{CO_2} in order to fully characterize the acid-base disorder. In patients with functioning fistulas or grafts, such a sample can simply be obtained from the arterial side of the cannulated access.

The Patient With a Persistently Low Serum [Total CO_2]

Dialysis patients with predialysis or steady-state serum [total CO_2] values less than 20 mEq/L are at increased risk for muscle catabolism and worsening renal osteodystrophy. Those with predialysis values less than 19 mEq/L have a higher mortality risk. In patients with a low predialysis serum [total CO_2], one should first assess whether the treatment is effectively increasing serum [total CO_2] by measuring a postdialysis level. In a small minority of patients, typically those with severe hypotension during the procedure, organic acid (presumably lactic acid) production can consume all of the added HCO_3^-.

If the treatment is effective, an assessment of dietary protein and fluid intake should be undertaken (patient characteristics in Table 33.1) and appropriate modifications instituted. If these measures fail, increasing bath [HCO_3^-] by 1–4 mEq/L can increase predialysis serum [total CO_2] in most patients, with the caveat that higher bath [HCO_3^-] may by itself increase mortality risk. An alternative therapy is daily oral sodium bicarbonate supplements. Management is more difficult in patients receiving peritoneal dialysis. If nutritional measures fail, oral bicarbonate therapy may help, or one can switch to a bicarbonate-containing peritoneal dialysis solution or hemodialysis.

The Patient With a Persistently High Serum [Total CO_2]

Predialysis serum [total CO_2] values > 26 mEq/L in patients receiving intermittent hemodialysis are associated with an increased mortality risk, but this risk appears to be largely due to nutritional and inflammatory factors rather than the prescribed dialysis treatment. Although many nephrologists lower bath [HCO_3^-] during hemodialysis in these patients,

there is no evidence to date indicating that such a change in prescription will benefit the patient. Instead, attention should be focused on the patient's nutrition and causes of inflammation. The same principle applies in patients receiving peritoneal dialysis; reducing bath [lactate] is unlikely to be beneficial.

Identifying Superimposed Acid-Base Disorders

The presence of a superimposed *metabolic* acid-base disorder in a patient receiving dialysis therapy can be brought to one's attention by a change or new abnormality in serum [total CO_2] (Fig. 33.3). By contrast, *respiratory* disorders can only be suspected from clinical signs and symptoms; serum [total CO_2] does not change notably. Serum [total CO_2] varies widely among dialysis patients. Fortunately, this parameter is usually measured on a regular basis, allowing a baseline for comparison. Assessment of a suspected new acid-base disorder involves the same three steps as in patients with functioning kidneys:

1. Identification of the primary disorder (i.e., metabolic acidosis or alkalosis, respiratory acidosis or alkalosis).
2. Assessment of the secondary response in order to determine whether the disorder is simple or mixed (simultaneous presence of two or more acid-base disorders).
3. Determination of the cause. For this last step, assessment of whether the anion gap has changed is useful, particularly when metabolic acidosis is present.

Steps 1 and 2 require measurement of arterial P_{CO_2} and pH and calculation of $[HCO_3^-]$. In patients with functioning fistulas or synthetic grafts, a separate arterial puncture is not required for this measurement. Blood from fistulas or grafts is equivalent to arterial blood.

Rules for Identification of the Primary Disturbance in Dialysis Patients

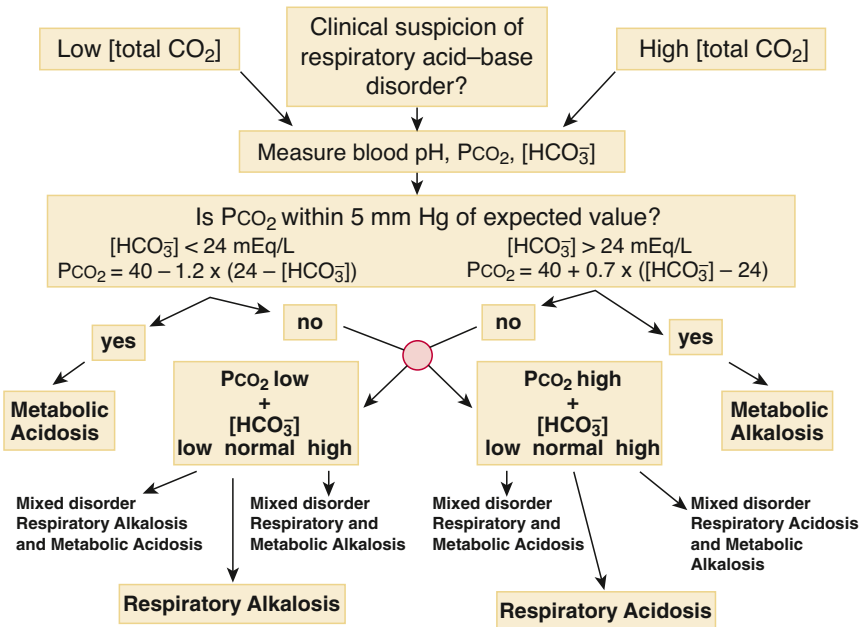
- New metabolic acidosis: Serum [total CO_2] lower than the usual value by 3 mEq/L or more.
- New metabolic alkalosis: Serum [total CO_2] higher than the usual value by 3 mEq/L or more.
- New respiratory acidosis: Arterial P_{CO_2} higher than predicted for the prevailing serum $[HCO_3^-]$ by 5 mm Hg or more (see equations following).
- New respiratory alkalosis: Arterial P_{CO_2} lower than predicted for the prevailing serum $[HCO_3^-]$ by 5 mm Hg or more (see equations following).

Evaluation of the Secondary Response

Arterial P_{CO_2} responds to changes in serum $[HCO_3^-]$ in dialysis patients in the same fashion as in individuals with normal kidney function. Thus, the rules of thumb are the same.

- For blood $[HCO_3^-] < 24$ mEq/L: Arterial P_{CO_2} (mm Hg) $= 40 - 1.2 \times (24 - \text{blood } [HCO_3^-])$
- For blood $[HCO_3^-] > 24$ mEq/L: Arterial P_{CO_2} (mm Hg) $= 40 + 0.7 \times (\text{blood } [HCO_3^-] - 24)$

In contrast to patients with functioning kidneys, blood $[HCO_3^-]$ does *not* change in response to primary changes in P_{CO_2}. As discussed previously, it is fixed primarily by the dialysis prescription and by endogenous acid production. Thus, there is no secondary change in blood $[HCO_3^-]$ in response to hypocapnia or hypercapnia.



• **Fig. 33.3** Approach to the Diagnosis of Acid–Base Disorders in Dialysis Patients. See text for definitions of high and low serum [total CO_2]. (Adapted from Gennari FJ. Acid–base considerations in end-stage renal disease. In: Henrich WL, ed. *Principles and Practice of Dialysis*. Baltimore: Lippincott, Williams, & Wilkins; 2003:402.)

Causes of Acid-Base Disorders

Metabolic Acidosis

A key management issue is to recognize the presence of a new acute metabolic acidosis, that is, a reduction in serum [total CO_2] (see previous rules for recognition). Once identified, assessment should include measurement of the anion gap, $[Na^+] - ([Cl^-] + [HCO_3^-])$, to determine whether it is increased. For this assessment, one should compare the value obtained with the most recent value prior to development of acidosis. The causes of metabolic acidosis are outlined in Table 33.4.

Virtually all of the causes of a superimposed metabolic acidosis in patients receiving dialysis therapy produce an increase in the anion gap. The most common cause is diabetic ketoacidosis. In contrast to patients with functioning kidneys, fluid and alkali replacement is unnecessary for treatment. In the absence of kidney function, no fluid or ketoanion losses occur. Insulin therapy rapidly leads to metabolism of the retained ketoanions, regenerating the HCO_3^- consumed, and quickly restores serum $[HCO_3^-]$ to the premorbid level. With other organic acidoses, dialysis removes the offending toxins and replenishes alkali stores quickly.

If the anion gap is not increased, only two causes need to be considered. The first is gastrointestinal alkali loss. Such losses are straightforward to diagnose and can be replaced rapidly by dialysis at the same time losses are curtailed by therapeutic intervention. The second is excessive fluid volume expansion with salt and water. As outlined in Table 33.2, predialysis serum [total CO_2] is inversely related to fluid retention between treatments. The effect is usually only a mild reduction in serum [total CO_2]. Iatrogenic volume expansion with isotonic saline in these patients will produce the same effect.

TABLE 33.4 Causes of Metabolic Acidosis in Dialysis Patients

Increased Anion Gap
Endogenous causes
Diabetic ketoacidosis
Lactic acidosis
Alcoholic ketoacidosis
Increased endogenous acid production (high protein intake or catabolic state)
Toxin ingestions
Methyl alcohol
Ethylene glycol
Salicylates
Paraldehyde
No Increase in Anion Gap
Gastrointestinal alkali loss
Expansion acidosis

Metabolic Alkalosis

A new metabolic alkalosis may be missed in patients receiving dialysis treatment because serum [total CO_2] may still be in the normal range for patients with functioning kidneys. For example, in a dialysis patient with a steady-state predialysis serum [total CO_2] of 21 mEq/L, a sudden increase to 26 mEq/L indicates the development of a metabolic alkalosis. Hypokalemia, a characteristic feature of metabolic alkalosis in patients with functioning kidneys, does not occur. Moreover, dialysis patients have no way to excrete excess alkali added to the body. Once metabolic alkalosis is induced, it is sustained by the dialysis procedure itself, which does not remove HCO_3^- unless serum [total CO_2] is greater than 35–40 mEq/L.

None of the renal causes of metabolic alkalosis (e.g., aldosterone adenoma, Bartter syndrome) produce this disorder in patients without kidney function. Metabolic alkalosis has two causes in dialysis patients: gastrointestinal HCl loss and excess alkali administration. The most common cause of metabolic alkalosis is vomiting or nasogastric suction. In patients without kidney function, such losses can lead to severe and sustained alkalosis. An increase in serum [total CO_2] may be the key to identifying the presence of bulimia in a dialysis patient.

A sometimes-overlooked cause is exogenous alkali administration. In addition to sodium bicarbonate ingestion (e.g., Alka-Seltzer, baking soda), a common source is organic anion administration. Citrate, lactate, acetate, and other organic anions given in various parenteral solutions can all increase serum [total CO_2]. Discontinuation or a reduction in the amount given will correct or ameliorate the disorder. Metabolic alkalosis in the intensive care unit is often caused by daily hemodialysis in patients with low rates of endogenous acid production, by excess HCO_3^-, or lactate replacement in patients receiving continuous renal replacement therapy. The combination of potassium binding resins and oral aluminum hydroxide can cause metabolic alkalosis by acting together to bind H^+ in the stomach.

Rapid reduction in serum [total CO_2] is rarely required for the treatment of metabolic alkalosis. Hemodialysis limits the increase to about 35 mEq/L unless H^+ losses are very large. If rapid removal is necessary, bath $[HCO_3^-]$ can be reduced to facilitate alkali loss during hemodialysis. Alternatively, one can institute continuous venovenous hemofiltration and use only saline for replacement fluid.

Respiratory Acidosis

Detection of respiratory acidosis requires clinical suspicion, and measurement of arterial pH and P_{CO_2} is necessary to confirm the diagnosis (Fig. 33.3). Serum [total CO_2] does not increase in response to hypercapnia in patients receiving dialysis therapy. Even the small increase normally engendered by the buffer response to

hypercapnia may be modified by the dialysis treatment. With the exception of the patient on a ventilator with fixed minute ventilation in whom an increase in CO_2 generation can increase arterial P_{CO_2}, respiratory acidosis is caused by pulmonary insufficiency. Thus, the first approach to management should always be an attempt to improve ventilation. If ventilation cannot be improved, increasing blood [HCO_3^-] can mitigate the acidemia. Bath [HCO_3^-] can be increased, or the patient switched to peritoneal dialysis to achieve this goal.

Respiratory Alkalosis

Hypocapnia induces severe alkalemia in patients receiving dialysis therapy because there is no secondary renal response, and the body buffer response is reversed by alkali addition during treatment. Blood pH values >7.70 have been observed. Diagnosis requires clinical suspicion and measurement of arterial pH and P_{CO_2}. Respiratory alkalosis has multiple causes, including hypoxemia, anxiety, central nervous system disease, pulmonary disease, and hepatic failure. Correction of the cause of the hypocapnia, if possible, is the first approach to treatment. If the alkalemia is severe (pH >7.65), arterial P_{CO_2} should be increased acutely using a rebreathing device. Sustained hypocapnia is more difficult to manage. The only option is to dialyze the patient against a bath with a low [HCO_3^-], but chronic hyperventilation is a very poor prognostic indicator, and no therapy is very effective.

Mixed Acid-Base Disorders

Two or more acid-base disorders can coexist in patients receiving dialysis therapy, but the occurrence of such mixed disorders is rare. Mixed disorders are diagnosed by demonstrating that the secondary response to a given acid-base disorder is either less than or greater than that predicted by the rules presented previously (Fig. 33.3). Table 33.5 lists the possible mixed disorders in dialysis patients. The importance of detecting the presence of more than one disorder lies in the approach to management. For example, the presence of metabolic acidosis (low serum [HCO_3^-]) and respiratory acidosis (arterial P_{CO_2} not appropriately reduced) requires that attention be directed to the patient's ventilatory status as well as correcting the metabolic acidosis.

TABLE 33.5 Mixed Acid–Base Disorders in Dialysis Patients

Mixed Metabolic and Respiratory Acid–Base Disorders
Metabolic acidosis [HCO_3^-] ↓
+ Respiratory acidosis P_{CO_2} ≥5 mm Hg or more above expected value*
+ Respiratory alkalosis P_{CO_2} ≤5 mm Hg or more below expected value
Metabolic alkalosis [HCO_3^-] ↑
+ Respiratory acidosis P_{CO_2} ≥5 mm Hg or more above expected value
+ Respiratory alkalosis P_{CO_2} ≤5 mm Hg or more below expected value

* See Fig. 33.3 for formulas defining appropriate P_{CO_2} for any given serum [HCO_3^-].

Recommended Reading

Feriani M. Use of different buffers in peritoneal dialysis. *Semin Dial.* 2000;13:256–260.

Acid–base measurements in patients receiving peritoneal dialysis, using either lactate or bicarbonate in the bath solution.

Gennari FJ. Effect of renal replacement therapy on acid–base homeostasis, and acid–base disorders in dialysis patients. In: Gennari FJ, Adrogué HJ, Galla JH, Madias NE, eds. *Acid–Base Disorders and Their Treatment.* New York: Taylor & Francis; 2005:697–730.

Complete discussion, fully referenced, of acid–base balance in both peritoneal and hemodialysis (and of acid–base disorders) in patients receiving dialysis therapy.

Sargent JA, Marano S, Marano M, Gennari FJ. Acid–base homeostasis during hemodialysis: new insights into the mystery of bicarbonate disappearance during treatment. *Semin Dial.* 2018;31:468–478.

Quantitative analysis of alkali addition to the ECF during hemodialysis and the patient response to it. During a routine hemodialysis treatment, almost 90% of the added bicarbonate is rapidly removed from the ECF by body buffers and an increase in organic acid production.

Tentori F, Karaboyas A, Robinson BM, et al. Association of dialysate bicarbonate concentration with mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis.* 2013;62(4):738–746.

A large international cohort study (11 countries) showing an increase in mortality risk of 8% for every 4mEq/L increase in bath [HCO_3^-] independent of pre-dialysis serum [HCO_3^-].

Uribarri J, Zia M, Mahmood J, et al. Acid production in hemodialysis patients. *J Am Soc Nephrol.* 1998;9:114–120.

Acid balance measurements in patients receiving conventional hemodialysis.

Wu DY, Shinaberger CS, Regidor DL, et al. Association between serum bicarbonate and death in hemodialysis patients: is it better to be acidotic or alkalotic? *Clin J Am Soc Nephrol.* 2006;1:70–78.

A large cohort study demonstrating the inverse relationship between protein catabolic rate and predialysis serum [HCO_3^-] in patients receiving conventional hemodialysis. The results show that the increased mortality risk associated with high predialysis values is due largely to malnutrition and inflammation rather than to the presence of alkalosis. By contrast, in patients with low values (<19mEq/L), the higher mortality risk is related to metabolic acidosis per se.

34

Nutritional Management of Hemodialysis Patients

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Introduction

One of the most encountered complications of end-stage kidney disease (ESKD), especially for patients undergoing maintenance hemodialysis (MHD), is the subtle but clinically important progressive deterioration of nutritional status. Advanced chronic kidney disease (CKD) is associated with a unique state of metabolic and nutritional derangements, more aptly called protein-energy wasting (PEW). PEW is closely associated with major adverse clinical outcomes, such as increased rates of hospitalization and death in MHD patients. PEW is complicated and includes a number of clinically relevant aspects that require special attention. These include, but are not limited to, how to appropriately screen and assess nutritional status, implement preventive measures, and prescribe effective interventions.

Screening and Assessment of Nutritional Status in Maintenance Hemodialysis

A clinically meaningful assessment of nutrition and metabolic status should be able to identify and risk-stratify patients with PEW, distinguishing the causes and consequences of both PEW and the underlying disease states, and determine whether there is potential benefit from nutritional or metabolic interventions. Therefore, no single nutritional marker is likely to adequately phenotype this highly complicated comorbid state requiring several concurrent or consecutive measurements (Table 34.1). It is recommended that MHD patients should undergo routine screening tests that are easy to perform, readily available, and inexpensive. Screening parameters should be collected routinely in clinical practice by any health professional and mostly provide a trigger to conduct a more extensive assessment to confirm or establish the diagnosis and determine the best course of treatment if needed. The most commonly used screening tests in MHD patients are serum albumin concentration and assessment of body weight, especially immediately following hemodialysis (i.e., estimated dry weight). Any clinically meaningful change in these metrics is adequate to initiate a more thorough workup. Nutritional assessment generally requires extensive training, provides comprehensive information to make a nutritional diagnosis, aid in intervention and monitoring planning, and should be performed by qualified individuals, preferably dietitians. The most commonly used tests in MHD patients include serum prealbumin concentration, assessment of dietary nutrient intake, anthropometric measures, and subjective global assessment (SGA). These tests should also be used for guiding nutritional therapies once the patient is deemed to be at risk or has overt PEW. A diagnosis of PEW necessitates confirmation by several tools and can be as strict as the requirement of multiple findings as suggested by the International Society of Renal Nutrition and Metabolism (ISRNM) criteria or could be less specific as suggested by others. It is also important that a number of considerations must be made on the unique situation of CKD patients for appropriate screening and assessment of their nutritional status. Some of these include the fluid status of the patient, which could alter body composition and biochemical markers; presence of systemic inflammation that could change serum concentrations of acute-phase proteins; presence and extent of proteinuria, a major determinant of serum albumin concentrations; and the level of residual kidney function, which could influence serum concentration of some biochemical markers such as prealbumin that are cleared by the kidneys. A simplified four-step PEW scoring, including serum creatinine/body surface area (Scr/BSA) and normalized protein nitrogen appearance (nPNA), was also suggested as an easy measure for nutritional assessment. In addition to biochemistry, body composition analysis via preferably by dual-energy x-ray absorptiometry can also be applied to selected patients, especially those whose volume status is unstable.

TABLE 34.1 Suggested Strategies to Screen and Assess Nutritional Status in Advanced CKD

Screening	Threshold for Detailed Assessment
Body weight	Continuous decline or <85% IBW
Dietary nutrient intake	DEI <25 kcal/kg IBW/day
	DPI <0.8 g/kg IBW/day
Serum albumin	<4.0 g/dL
Serum creatinine	Relatively low value
MST	>2
Assessment	**Threshold for Intervention**
Serum prealbumin	<28 mg/dL
hsCRP	>10 mg/dL
Anthropometrics	Deviation from norms
SGA	B or C (moderately or severely malnourished)
MIS	>5
Diagnosis (2 of the 4) *	**Threshold for Intervention**
Serum Chemistry	
Albumin	<3.8 g/dL
Prealbumin	<28 mg/dL †
Cholesterol	<100 mg/dL
Body Mass	
BMI	<23
Weight loss	>5% over 3 months or 10% over 6 months
Total body fat %	<10%
Muscle Mass	
Muscle wasting	>5% over 3 months or 10% over 6 months
Reduced MAMC	>10% reduction compared to norms
Creatinine appearance	<1 g/kg/IBW
Dietary Intake	
Low DPI	DPI <0.8 g/kg IBW/d
Low DEI	DEI <25 kcal/kg IBW/d

* Based on International Society of Nutrition and Metabolism Criteria (Fouque D, Kalantar-Zadeh K, Kopple J, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int.* 2008;73:391–398.).
† Influenced by kidney function.
BMI, Body mass index; *CKD*, chronic kidney disease; *DEI*, dietary energy intake; *DPI*, dietary protein intake; *hsCRP*, high-sensitivity C-reactive protein; *IBW*, ideal body weight; *MAMC*, mid-arm muscle circumference; *MIS*, malnutrition–inflammation score; *MST*, Malnutrition Screening Tool; *SGA*, subjective global assessment.
Adapted from Ikizler TA. A patient with CKD and poor nutritional status. *Clin J Am Soc Nephrol*. 2013;8:2174–2182.

Epidemiology of Protein-Energy Wasting in Maintenance Hemodialysis Patients

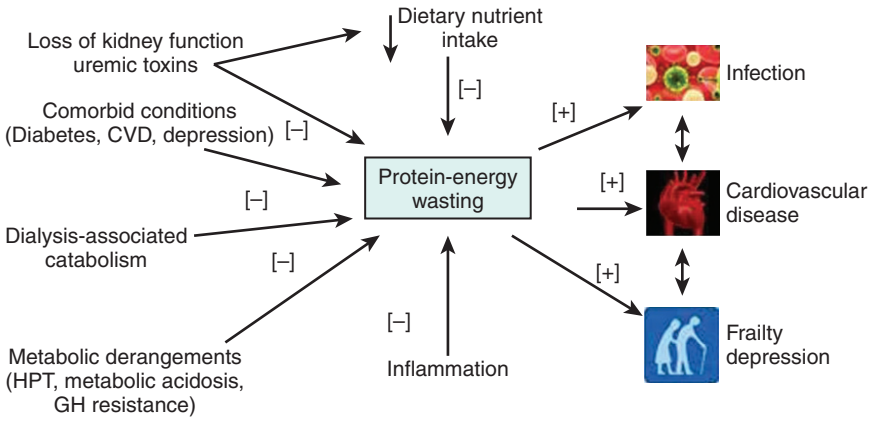
Virtually every study evaluating the nutritional status of MHD patients reports some degree of protein and energy depletion. The clinical relevance of these observations is that practically every nutritional marker used in this patient population has been associated with hospitalization and death risk. Of note, most of the epidemiologic reports on nutrition in MHD patients have been mainly based on serum albumin concentrations, especially studies in large cohorts. Smaller studies using other nutritional markers such as serum prealbumin and SGA also are suggestive of increased risk associated with poor nutritional status in MHD patients. These observations are reproducible irrespective of patient demographics and geographic area. Because of the many different diagnostic tools utilized in separate studies, the prevalence of PEW in this patient population varies widely among different reports, ranging from 20% to 60%. Although there is evidence of improvement in nutritional parameters within 3 to 6 months following initiation of MHD, PEW is still present in up to 40% or more of those patients, and the prevalence seems to increase as the time on dialysis extends. Epidemiologic data also indicate a survival benefit with improvement in these markers over time.

A comprehensive meta-analysis composed of 90 studies from 34 countries reported a heterogeneous global distribution of PEW prevalence in MHD patients ranging from 28% to 54% throughout the world. Crude prevalence in the United States was reported to be as high as 80%, whereas most studies from Europe reported PEW in approximately 50% of patients with CKD. There was a wide range reported in Asia, 18%–>80%, probably due to the methods used to define PEW. Of note, the geographical region was identified as a significant determinant explaining 23% of heterogeneity worldwide.

In addition to mortality, a number of studies show significant associations between nutritional markers and several patient-reported outcomes such as fatigue, physical performance, and frailty. Studies reported that serum albumin levels are negatively correlated with fatigue and lower muscle mass. Low body mass index (BMI) is also associated with muscle loss and sarcopenia in MHD patients. Overall, epidemiological data suggest that inadequate nutrition stores are associated with frailty and decreased quality of life in MHD patients.

Etiology and Prevention of Protein-Energy Wasting in Maintenance Hemodialysis Patients

Multiple factors affect nutritional and metabolic status in patients undergoing MHD that lead to adverse consequences (Fig. 34.1). Accordingly, prevention and treatment



• **Fig. 34.1** The Etiology and Consequences of Protein-Energy Wasting in Kidney Disease. *CVD*, Cardiovascular disease; *GH*, growth hormone; *HPT*, hyperparathyroidism.

of PEW in patients on MHD should involve an integrated approach to reduce protein and energy depletion along with interventions that will avoid further losses and replenish already wasted stores.

Dietary Nutrient Intake

A frequent and important cause of PEW in patients undergoing MHD is inadequate dietary protein and energy intake relative to the needs, primarily due to "uremic" anorexia. The spontaneous decrease in dietary protein and energy intake were seen in nondialysis CKD patients usually improves once maintenance dialysis is commenced. Nevertheless, a significant portion of MHD patients could still suffer from anorexia as a result of inadequate dialysis and retention of uremic toxins, intercurrent illnesses, chronic systemic inflammation, and depression. Some of the dietary restrictions implemented prior to initiation of maintenance dialysis are often continued in an attempt to prevent hyperphosphatemia, hyperkalemia, or metabolic acidosis. It is therefore imperative to continuously reassess ESKD patients once they are initiated on maintenance dialysis to prevent and treat the root cause of PEW prior to prescribing aggressive nutritional supplementation.

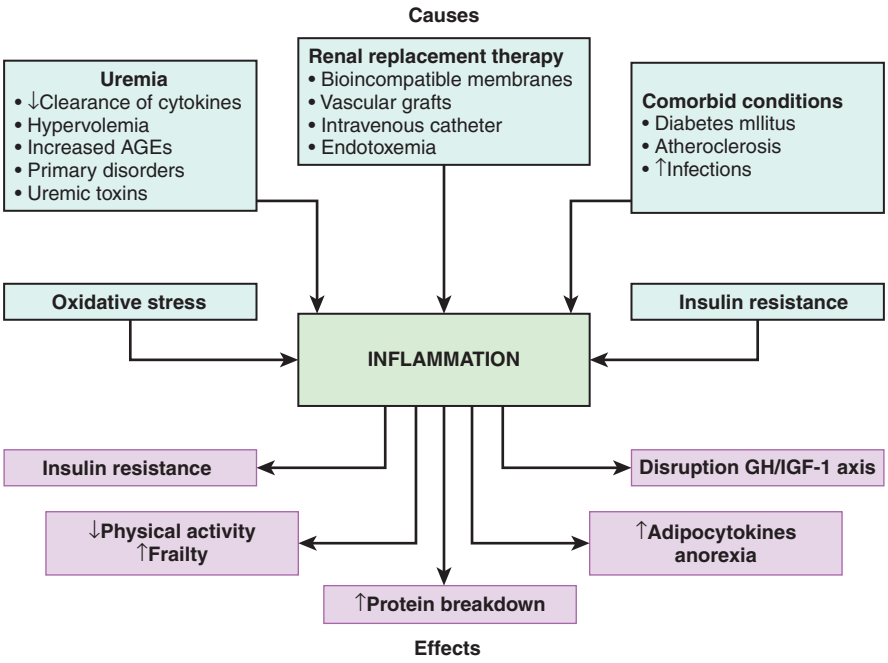
Increased Catabolism Due to Renal Replacement Therapy

Provision of an adequate dialysis dose has long been considered as a cornerstone among measures to prevent and treat PEW in maintenance dialysis patients, and a minimum dose of dialysis has been recommended to avoid uremic anorexia and maintain optimal dietary nutrient intake. Data from randomized controlled trials (RCTs) in MHD (HEMO study) and peritoneal dialysis (PD) (ADEMEX Trial) patients indicate that what is currently considered adequate dialysis in various guidelines is sufficient to preserve the nutritional status, although the HEMO study showed that MHD patients lose weight over time regardless of "adequate" dialysis dose. Increasing dialysis dose beyond the targets studied in these trials has not been shown to improve nutritional status any further. In addition, in the HEMO and Membrane Permeability Outcome trials, most nutritional parameters studied did not differ among patients exposed to different dialysis membranes (i.e., high flux vs. low flux), although there was a nominally significant survival benefit in patients with baseline serum albumin levels <40 g/dL (prespecified analysis) and with diabetes mellitus (DM) (post hoc analysis) randomized to high-flux dialysis in the latter. The results of the Frequent Hemodialysis Network Trial indicate no appreciable difference in nutritional markers between subjects randomized to six times a week in-center HD versus standard three times a week in-center HD.

Nutrient losses through hemodialysis membranes (6–8 g per HD session), loss of residual kidney function, increased systemic inflammation due to indwelling catheters, use of bioincompatible hemodialysis membranes, and peritoneal dialysis solutions could also lead to an overly catabolic milieu and increase the minimal amount of nutrient intake needed to maintain a neutral nitrogen balance and, hence, acceptable nutritional stores. In patients who cannot compensate for this increased need, a state of semistarvation ensues, leading to the development or worsening of PEW. One potential strategy to prevent the immediate protein catabolic effects of hemodialysis is to allow stable patients to consume a reasonable number of regular meals during hemodialysis. This practice has been shown to be safe in multiple settings and is a routine process except in a few countries such as the United States and Canada.

Chronic Systemic Inflammation

Systemic inflammation is a major contributor to PEW in patients undergoing MHD (Fig. 34.2). Increased systemic levels of inflammatory cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha (TNF-α) play a crucial role in exaggerated protein and energy catabolism, resulting in sarcopenia and frailty in chronic disease states. Despite convincing data in animals, there are very limited studies examining the mechanisms and nature of inflammation-induced catabolism in MHD patients. In addition to increasing protein breakdown, the chronic inflammatory state is associated



• **Fig. 34.2** Proposed Etiology of Systemic Inflammation in Kidney Disease and Its Adverse Effects Leading to Protein-Energy Wasting. *AGE*, advanced glycation endproducts; *GH*, growth hormone; *IGF-1*, insulin-like growth factor 1.

with reduced physical activity and impaired anabolic actions of insulin and growth hormone (GH) and may also contribute to anorexia because of its central effects.

The initial step for the treatment of persistent inflammation should be the elimination of etiologic factors such as the use of central hemodialysis catheters in MHD patients. As the dialysis procedure per se might stimulate the immune system, the proinflammatory effects of dialysis membranes and fluids should also be taken into account in maintenance dialysis patients. Many uremic toxins are also known to be proinflammatory. Current dialytic strategies are inadequate for their removal, and alternative removal techniques, such as strategies to modify intestinal generation or absorption, could be considered. Volume overload leads to immunoactivation and increased cytokine production via bacterial or endotoxin translocation. Recent data suggest excessive accumulation of salt in the muscle compartment of patients undergoing MHD, which in itself contributes to local and systemic inflammation. Therefore, appropriate management of fluid and electrolyte status might improve systemic inflammation in ESKD patients.

Metabolic Acidosis and Hormonal Derangements

Metabolic acidosis is associated with increased muscle protein catabolism and promotes PEW in patients with advanced CKD. There are a number of studies indicating an improvement in nutritional status with oral bicarbonate supplementation in CKD patients. Recent epidemiologic data indicate adverse outcomes with high predialysis serum bicarbonate levels, requiring a target of 24–26 mmol/L in MHD patients in order to avoid alkalosis after hemodialysis.

Resistance to insulin and the GH/insulin-like growth factor 1 (IGF-1) axis are two key endocrine abnormalities implicated in the loss of muscle mass in CKD patients. Enhanced protein catabolism applies to both insulin-deficient and insulin-resistant states. MHD patients with suboptimally controlled type 2 diabetes have a higher rate of muscle protein loss than MHD patients without diabetes, a catabolic state that can be detected even in MHD patients with insulin resistance. A high prevalence of other metabolic and hormonal disorders such as increased parathyroid hormone concentration, low levels of testosterone, and several abnormalities in thyroid hormone profile might also increase hypermetabolism and decrease anabolism, leading to excess catabolism in MHD patients.

Comorbidities in Chronic Kidney Disease

CKD patients often have other comorbid diseases that can adversely affect nutritional status. Patients with CKD secondary to DM have a higher incidence of PEW when compared to non-DM patients. The degree of insulin resistance and/or insulin deprivation seems to play the most critical role in this process. CKD patients are also likely to suffer protein depletion because of associated gastrointestinal disturbances (e.g., diabetic gastroparesis, nausea and vomiting, bacterial overgrowth in the gut and pancreatic insufficiency, impaired protein absorption in the gut). Polypharmacy worsens these gastrointestinal complications. Appropriate management of these disturbances, along with an emphasis on oral health, especially in the elderly, is critical to maintain optimal oral nutrient intake.

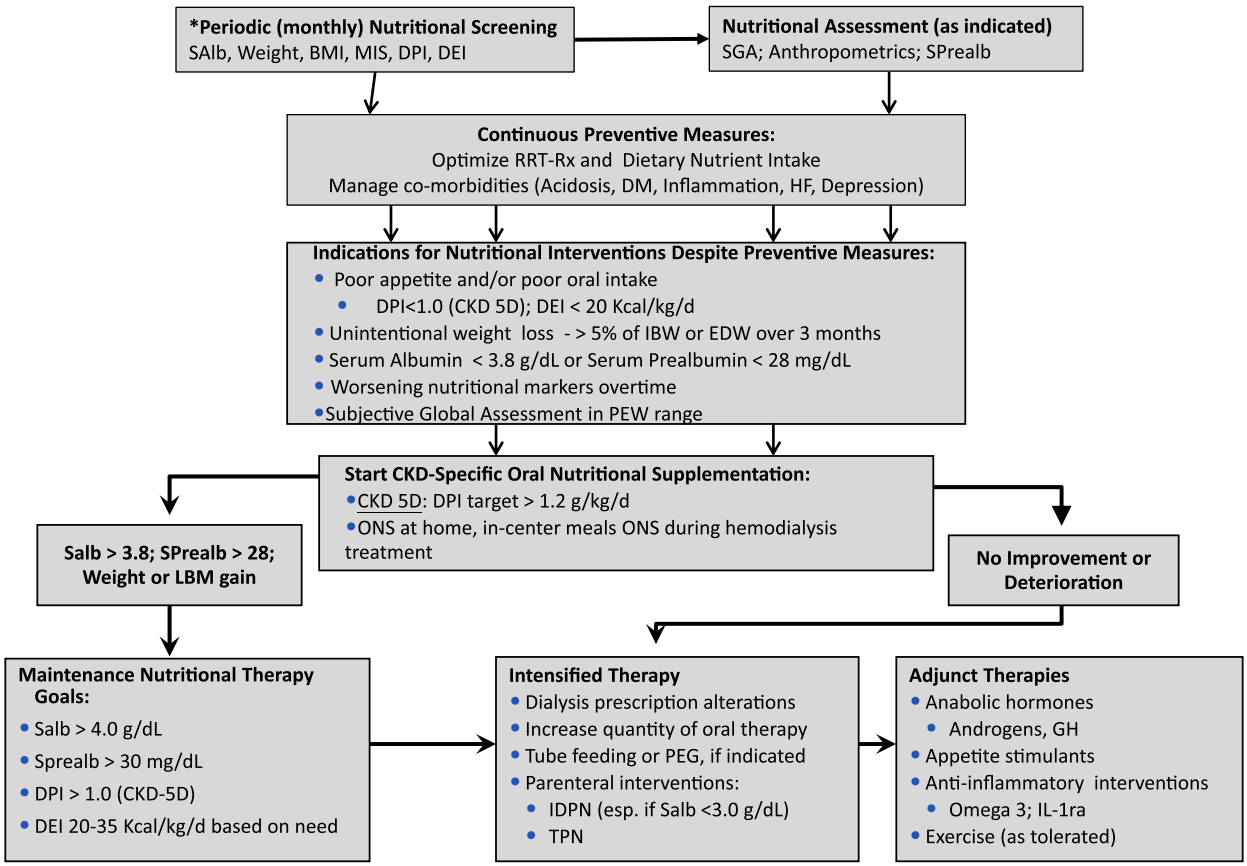
Based on the multiple catabolic stimuli associated with advanced CKD and renal replacement therapies, the

minimum dietary protein requirements for MHD patients who are metabolically stable is 1.0–1.2 g/kg body weight per day. The recommended dietary intake to maintain normal nutritional status for patients on MHD is 25–35 kcal/kg ideal body weight per day based on age, gender, level of physical activity, body composition, weight status goals, and concurrent illness or presence of inflammation. Furthermore, it is important that at least 50% of the protein intake should be of high biologic value. An important consideration regarding strategies to improve dietary protein intake in MHD patients is the potential increase in the intake of several potentially harmful elements, especially phosphorus. Dietary recommendations to improve protein intake should take into account the phosphorus content of the specific protein sources (i.e., vegetarian diet leading to lower serum phosphorus levels) and other phosphorus-containing nutrients, especially ones with additives/preservatives in processed food.

Treatment of Protein-Energy Wasting in Maintenance Hemodialysis Patients

Oral and Enteral Nutritional Supplementation

In certain MHD patients, the aforementioned standard preventive measures are unable to diminish the loss of protein and energy stores. In these circumstances, nutritional supplementation is a suitable next step with appropriate indications (Fig. 34.3). Oral supplementation should be given two to three times a day, preferably at least 2 hours before or after main meals and/or during dialysis for MHD patients. Oral supplementation can provide an additional 7–10 kcal/kg per day of energy and 0.3–0.4 g/kg per day of protein. This requires a minimum spontaneous dietary intake of 20 kcal/kg per day of energy and 0.4–0.8 g/kg per day of protein in order to meet the recommended dietary energy intake (DEI) and dietary protein intake (DPI)



• **Fig. 34.3** Algorithm for nutritional management and support in patients with chronic kidney disease. *Minimum every 3 months, monthly screening recommended. ^Only for end-stage renal disease patients without residual renal function. *BMI*, Body mass index; *CHF*, congestive heart failure; *CKD*, chronic kidney disease; *DEI*, dietary energy intake; *DM*, diabetes mellitus; *DPI*, dietary protein intake; *GH*, growth hormone; *IDPN*, intradialytic parenteral nutrition; *IL-1ra*, interleukin-1 receptor antagonist; *LBM*, lean body mass; *MIS*, malnutrition–inflammation score; *ONS*, oral nutritional supplement; *PEG*, percutaneous endoscopic gastrostomy; *PEW*, protein-energy wasting; *RRT-Rx*, renal replacement therapy prescription; *SAlb*, serum albumin (measured by bromocresol green); *SGA*, subjective global assessment; *SPrealb*, serum prealbumin; *TPN*, total parenteral nutrition. (Used with permission from Ikizler TA, Cano NJ, Franch H, et al. Prevention and treatment of protein-energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. *Kidney Int*. 2013;84(6):1096–1107.)

targets. Clearly, additional nutrient intake is necessary to meet the aforementioned goals.

The efficacy of oral supplementation has been studied in multiple settings. The beneficial nutritional effects of these supplements ranged from improvements in serum biomarkers such as albumin, prealbumin, and transferrin to gains in different body compartments such as weight and lean body mass. The effects were evident as early as within a month and were sustained in most, if not all, studies. There were also improvements in quality of life and physical functioning. In several of these studies, improvements in hospitalizations and death were reported, but none of the studies had the statistical power to assess the efficacy of these interventions appropriately. For patients who are unable to tolerate nutritional supplementation by mouth, nasogastric tubes, percutaneous endoscopic gastroscopy, or jejunostomy tubes can be considered. Tube feeding is most often used in conditions such as severe anorexia, swallowing troubles secondary to neurologic or head and neck diseases, perioperative periods, and stress.

Several large-scale observational studies reported significant survival benefits in favor of hypoalbuminemic MHD patients receiving nutritional supplementation versus similarly matched controls. In a retrospective cohort study of 4289 matched pairs, death rates were 30.9% versus 37.3% in treated versus historically matched untreated groups, respectively. In a prospective observational study, the effects of an oral nutritional supplementation (ONS) program performed as part of a disease management plan were reported in 276 MHD patients who received supplements versus 194 MHD patients but did not receive ONS because they were deemed inappropriate or refused. ONS use was associated with higher serum albumin and lower hospitalization at 1 year, but there was no significant reduction in mortality risk in this study. The limitations of these studies include their retrospective design, convenience sampling, and residual confounding from unmeasured variables. Parenteral provision of nutrients, especially during the HD procedure (i.e., intradialytic parenteral nutrition [IDPN]), has been shown to be a safe and convenient approach for individuals who cannot tolerate oral or enteral administration of nutrients (see Chapter 36).

Anabolic Hormones

Recombinant human GH (rhGH), an approved treatment for short stature in pediatric CKD patients, leads to improved growth, confirming that rhGH could overcome the GH resistance associated with CKD. In adults with CKD, resistance to native GH may be responsible for the premature decline in body composition. In a large multicenter RCT, significant decreases were observed in C-reactive protein (CRP) and homocysteine levels along with increases in serum high-density lipoprotein (HDL) cholesterol and transferrin levels in hypoalbuminemic MHD patients in the rhGH group. This large RCT was prematurely terminated due to slow recruitment, without the ability to assess the effects that rhGH has on hospitalization or death.

Testosterone deficiency is also very common in male MHD patients and is associated with increased mortality risk and muscle function. Several RCTs performed in MHD patients showed significant benefits of nandrolone decanoate (ND) treatment on both anthropometric and biochemical parameters, including body weight, BMI, skinfold, mid-arm muscle circumference (MAMC), and serum levels of total protein, prealbumin, and transferrin. No consistent effect of ND was demonstrated on physical functioning in several studies, and high-dose ND (100 mg/week) was poorly tolerated in females because of its virilizing effects. In clinical practice, anabolic steroids could be used for preventing sarcopenia, albeit under close supervision, and such use should be limited to 6 months.

Exercise

Abnormalities in muscle function, exercise performance, and physical activity begin in the early stages of CKD and progress dramatically as ESKD develops. In MHD patients, there are metabolic and structural muscle abnormalities, with reductions in oxidative capacity and type 1 fibers with an associated decrease in muscular endurance. Recent data show the development of mitochondrial dysfunction in patients with advanced kidney disease, with patients on MHD displaying the worst abnormalities. Although a number of studies have examined the effects of cardiopulmonary fitness training in MHD patients, relatively few studies have examined the role of exercise training on stimulating muscle growth and improving muscle function. Collectively, the available data indicate that the presumed beneficial effects of exercise, such as improvements in muscle quality and quantity, strength, and physical functioning, are not consistently observed in ESKD patients. The possible explanations for the limited efficacy of exercise in CKD patients include the limitations of methods to assess body composition, inadequate intensity and/or duration of exercise, and the lack of understanding of the actual metabolic and morphologic abnormalities related to PEW in the setting of advanced CKD.

Emerging Therapies

Anti-inflammatory Agents

The fact that systemic inflammation leads to an exaggerated protein catabolic response has suggested that treatment with specific and nonspecific anti-inflammatory agents as a novel strategy to prevent the development or worsening of PEW in patients on MHD might be effective. Although a limited number of studies have shown the beneficial effects of these approaches on markers of systemic inflammation, only a few have extended these to nutritional outcomes. Biolo et al. investigated the effect of pentoxifylline on whole-body protein turnover, reported a significant decrease in protein breakdown, and also a net positive anabolic effect when pentoxifylline was combined with amino acid administration. A recent RCT, including 84 hypoalbuminemic HD patients, showed that 16 weeks of intervention resulted in a slight increase in serum albumin levels in the pentoxifylline arm. Tietze et al. documented that the administration

of supplemental fish oil (8 g daily) up to 6 months somewhat improved nutritional status. Another pilot study of 3 g daily of omega-3 administration showed significant improvements in protein breakdown rates in MHD patients. Although current data are intriguing, further long-term studies are warranted to determine the reproducible effects of anti-inflammatory strategies on the prevention or treatment of PEW in advanced CKD patients.

Appetite Stimulants

Ghrelin is a stomach-derived GH-releasing hormone that stimulates appetite via the central nervous system. Administration of ghrelin has been shown to increase muscle mass in experimental animal studies. Longer-term ghrelin administration resulted in net positive energy balance in an elderly population, demonstrating that it may be an alternative agent for the treatment of PEW in CKD patients. In animal models of CKD, ghrelin administration resulted in increased appetite and decreased muscle protein degradation. In a pilot study, the administration of subcutaneous ghrelin resulted in increased appetite in nine PD patients with PEW, suggesting that future clinical trials of longer-term administration of ghrelin could reveal intriguing results in advanced CKD patients at risk for PEW. Appetite stimulants such as megestrol acetate, melatonin, cyproheptadine, and dronabinol have long been used for improving appetite in MHD patients, although their efficacy has not been systematically examined.

Summary and Recommendations

Preservation of muscle mass and function is an important goal in the management of PEW in MHD patients. In MHD patients, in whom a number of catabolic signals dominate, it is critical to maintain a dietary protein and energy intake relative to needs. Preemptive treatment of concurrent conditions that contribute to catabolism, such as metabolic acidosis, insulin resistance, and systemic inflammation, is of paramount importance for the prevention of PEW. When supplemental nutrition is indicated, it is crucial to take into account all the determinants of body and muscle mass: protein and energy content, exercise, anabolizing hormones, antioxidants, anti-inflammatory nutrients or drugs, and other specific nutrients. Finally, it is important to assess the impact of nutritional supplements not only in terms of changes in nutritional parameters but also to translate these observations into potential improvements in multiple domains such as patient-reported outcomes, including quality of life and physical function, hospitalization, mortality, and cost-effectiveness.

Recommended Reading

Carrero JJ, Stenvinkel P, Cuppari L, et al. Etiology of the protein-energy wasting syndrome in chronic kidney disease: a consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM). *J Ren Nutr.* 2013;23:77–90.

An updated and comprehensive review of etiology of PEW in kidney disease.

Carrero JJ, Thomas F, Nagy K, et al. Global prevalence of protein-energy wasting in kidney disease: a meta-analysis of contemporary observational studies from the International Society of Renal Nutrition and Metabolism. *J Ren Nutr.* 2018;28:380–392.

This meta-analysis provides comprehensive information on the prevalence of protein-energy wasting across the range of kidney disease. This evidence-based dataset suggests PEW is a common phenomenon across the spectrum of AKI and CKD with some diversity based on geographical regions.

Fouque D, Kalantar-Zadeh K, Kopple J, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int.* 2008;73:391–398.

A consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM) regarding the nomenclature and diagnostic criteria for PEW in CKD patients.

Ikizler TA, Burrowes Jerrilynn, Byham-Gray Laura, et al. KDOQI clinical practice guideline for nutrition in chronic kidney disease: 2020 update. *Am J Kidney Dis.* 2020;76(3 Suppl 1):S1–S107.

This updated guideline document reflects the many changes in both guideline development and the management of nutritional aspects of CKD within the last 20 years. It is a comprehensive document that provides a comprehensive assessment of nutrition in all adult patients with CKD and includes recommendations on assessment, prevention, and treatment of PEW.

Ikizler TA. A patient with CKD and poor nutritional status. *Clin J Am Soc Nephrol.* 2013;8:2174–2182.

A case-based approach to a CKD patient transitioning from CKD to end-stage renal disease regarding nutritional and metabolic complications.

Ikizler TA, Cano NJ, Franch H, et al. Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. *Kidney Int.* 2013;84:1096–1107.

This is a comprehensive review of the potential benefits of providing nutrients during hemodialysis in order to counteract the catabolic effects of the procedure.

Lacson Jr E, Wang W, Zebrowski B, Wingard R, Hakim RM. Outcomes associated with intradialytic oral nutritional supplements in patients undergoing maintenance hemodialysis: a quality improvement report. *Am J Kidney Dis.* 2012;60:591–600.

This retrospective study provides the most significant evidence to indicate that ONS during hemodialysis potentially provides a mortality benefit in prevalent MHD patients. Similar retrospective data have been published subsequently by others confirming these associations.

Pupim L, Martin CJ, Ikizler TA. Assessment of protein-energy nutritional status. In: Kopple JD, Massry SG, eds. *Nutritional Management of Renal Disease.* 3rd ed. Waltham: Elsevier; 2013:137–158.

A detailed review of the methods used to assess nutrition status in CKD patients.

Roshanravan B, Gamboa J, Wilund K. Exercise and CKD: skeletal muscle dysfunction and practical application of exercise to prevent and treat physical impairments in CKD. *Am J Kidney Dis.* 2017;69:837–852.

This review focuses on the impact of kidney disease on skeletal muscle dysfunction in the context of the disablement process and reviews screening and treatment strategies that kidney health professionals can use in clinical practice to prevent functional decline and disability.

35

Intradialytic Parenteral Nutrition and Intraperitoneal Nutrition

RAMANATH DUKKIPATI, MD • ANNAMARIE RODRIGUEZ, RDN, LD, FAND • KAMYAR KALANTAR-ZADEH, MD, MPH, PhD

Introduction

Protein-energy wasting (PEW) is common in patients undergoing dialysis and is associated with one of the strongest risk factors for death. The prevalence of PEW in observational studies ranges from 18% to 75%. PEW is indicated by decreased body mass index (BMI) and muscle mass, reduced serum levels of albumin and transthyretin, increased markers of inflammation, and decreased food intake and appetite. The Centers for Medicare and Medicaid's End-Stage Kidney Disease (ESKD) Program Interpretive Guidance provides the most recent regulation related to the Conditions for Coverage for ESKD Facilities. The Measures Assessment Tool recommends serum albumin levels of at least 4.0 g/dL. Although the role of serum albumin levels continues to be debated, it remains a prognostic indicator of mortality and morbidity. Published trials have revealed that the implementation of nutrition interventions in chronic kidney disease (CKD) patients increased albumin levels an average of 0.2 g/dL, and this change reduced mortality rate, hospitalizations, and treatment costs. Lacson et al. hypothesized that increasing albumin by 0.2 g/dL would save $36 million in Medicare associated with a decrease in > 6000 hospitalizations and averting > 21,000 hospital days.

Inflammatory mediators negatively impact hepatic protein synthesis with both increased cytokines and positive acute-phase proteins and decreased negative acute-phase proteins. Protein catabolism, lipolysis, and anorexia are consequences of the inflammatory response mechanism. The Malnutrition-Inflammation Score (MIS) had been developed using the subjective global assessment (SGA), BMI, albumin, and total iron-binding capacity (TIBC). MIS has 10 components that are scored based on four levels of severity from 0 (normal) to 3 (very severe); see the MIS sheet in Fig. 35.1. Use of the MIS, C-reactive protein (CRP), and interleukin-6 (IL-6) correlated with the greatest risk of death and hospitalization in a study that included 378 CKD patients; it was suggestive that the tool might circumvent the need for expensive inflammatory assays. Ho et al. found that an MIS of 3, 4, or 5 was associated with a 10%, 40%, or 80% probability of death within a year, respectively, in hemodialysis patients. Additional data showed the MIS to be positively correlated with peritonitis, hospitalizations, erythropoiesis-stimulating agent (ESA) dosage requirements, and levels of CRP and ferritin in peritoneal dialysis (PD) patients.

Inadequate protein and energy intake and inflammatory disorders are the most common and dominant causes of PEW in maintenance dialysis patients. Nutrition assessment must incorporate both subjective and objective data. CKD patients are unique in their needs as they are faced with a complex paradigm of treatment that is ever shifting. The intuitive health care provider will take care to identify the patient PEW status and distinguish between malnutrition and inflammation to facilitate nutrition repletion. This led to the hypothesis that nutritional support can potentially prevent or stunt PEW and can also improve quality of life along with a reduction of morbidity and mortality. Unintentional weight loss harbors increased mortality over time, but increasing nutritional intake has not been shown to reduce mortality risk in randomized prospective clinical trials. Nevertheless, the search for interventions to reduce high mortality in dialysis patients is of utmost importance in changing the natural history of survival in these patients.

Intradialytic Parenteral Nutrition

Intradialytic parenteral nutrition (IDPN) solutions, an alternate feeding modality when enteral nutrition (EN) is insufficient to meet the patient's requirements, are commonly prepared from base substrates. The base solutions for amino acids, carbohydrates, and lipids can vary in concentrations. Up to 20% of essential and nonessential amino acids, 50% or 70% D-glucose, and 10% to 20% lipids or IDPN can also be prepared lipid free. Additives such as trace elements,

COMPREHENSIVE MALNUTRITION INFLAMMATION SCORE			
(A) Patients' related medical history:			
1- Change in end dialysis dry weight (overall change in past 3-6 months):			
0	1	2	3
No decrease in dry weight or weight loss <0.5 kg	Minor weight loss (≥0.5 kg but <1 kg)	Weight loss more than one kg but <5%	Weight loss >5%
2- Dietary intake:			
0	1	2	3
Good appetite and no deterioration of the dietary intake pattern	Somewhat sub-optimal solid diet intake	Moderate overall decrease to full liquid diet	Hypo-caloric liquid to starvation
3- Gastrointestinal (GI) symptoms:			
0	1	2	3
No symptoms with good appetite	Mild symptoms, poor appetite or nauseated occasionally	Occasional vomiting or moderate GI symtoms	Frequent diarrhea or vomiting or severe anorexia
4- Functional capacity (nutritionally related functional impairment:			
0	1	2	3
Normal to improved functional capacity, feeling fine	Occasional difficulty with baseline ambulation, or feeling tired frequently	Difficulty with otherwise independent activities (e.g. going to bathroom)	Bed/chair-ridden, or little to no physical activity
5- Co-morbidity including number of years on Dialysis:			
0	1	2	3
On dialysis less than one year and healthy otherwise	Dialyzed for 1-4 years, or mild co-morbidity (excluding MCC*)	Dialyzed >4 years, or moderate co-morbidity (including one MCC*)	Any severe, multiple co-morbidity (2 or more MCC*)
(B) Physical Exam (according to SGA criteria):			
6- Decreased fat stores or loss of subcutaneous fat (below eyes, triceps, biceps, chest):			
0	1	2	3
Normal (no change)	mild	moderate	Severe
7- Signs of muscle wasting (temple, clavicle, scapula, ribs, quadriceps, knee, interosseous):			
0	1	2	3
Normal (no change)	mild	moderate	Severe
(C) Body mass index:			
8- Body mass index: BMI = Wt(kg) / Ht^2(m)			
0	1	2	3
BMI≥20 kg/m^2	BMI: 18-19.99 kg/m^2	BMI: 16-17.99 kg/m^2	BMI<16 kg/m^2
(D) Laboratory Parameters:			
9- Serum albumin:			
0	1	2	3
Albumin≥ 4.0 g/dL	Albumin: 3.5-3.9 g/dL	Albumin: 3.0-3.4 g/dL	Albumin: <3.0 g/dL
10- Serum TIBC (total Iron Binding Capacity): ♣			
0	1	2	3
TIBC> 250 mg/dL	TIBC: 200-249 mg/dL	TIBC: 150-199 mg/dL	TIBC: <150 mg/dL
Total Score = sum of above 10 components (0-30)			

*MCC (Major Comorbid Conditions) include CHF class III or IV, full blown AIDS, severe CAD, moderate to severe COPD, major neurological sequlae, and metastatic malignancies or s/p recent chemotherapy.
♣Suggested equivalent increments for serum transferrin are: >200 (0), 170-199 (1), 140-169 (2), and <140 mg/dl

• **Fig. 35.1** The Malnutrition-Inflammation Score, also known as MIS, for nutritional grading of dialysis patients.

vitamins, and selected minerals can be included in the IDPN. IDPN solutions can be tailored to individual patient needs with specific consideration to visceral protein status, treatment goals, dialysis treatment, weight, presence of comorbid conditions (for example, diabetes and liver disease), and lipid levels. Although IDPN alone is insufficient to meet the estimated protein and energy needs of the patient, it does, however, enable the health care provider to provide consistent protein and kcalories with prescribed dialysis sessions to supplement a patient's enteral intake during either in-center hemodialysis or home hemodialysis (ICHD/HHD) therapy. A multitude of variables affects patients with CKD nutritional status to include uremia, derangements in metabolism, chronic metabolic acidosis, and additional comorbid diseases such as diabetes mellitus that affect the patient's capacity to utilize nutrients.

In addition, socioeconomic and cultural factors, food intolerances, and disparities in health care access play a role in patient outcomes, as well as language barriers potentially hindering nutrition education. These factors, and more, lend to an impaired intake of nutrients further compromised from the catabolic dialysis process itself. The catabolic effects of dialysis and the impact on the patient's nutritional needs are well documented. Patients undergoing hemodialysis may lose approximately 10–12 g of protein per dialysis session in addition to water-soluble vitamins and trace elements; thus, IDPN potentially thwarts this catabolic effect. When IDPN is given, it is initiated typically at the beginning of hemodialysis and is infused into the venous line distal to the hemodialyzer without the need to create additional vascular access. The infusion is usually planned to complete at about 15 to 30 minutes before the end of the hemodialysis session. Infusion rates of IDPN are presented in Table 35.1, and the typical components of IDPN solution are presented in Table 35.2. Components of commonly prescribed oral nutritional supplements and modular products are presented in Tables 35.3 and 35.4, respectively.

TABLE 35.1 Typical IDPN Formulations with Substrate Utilization Rates

Dextrose	Lipids	Protein (g/kg BW*)
Moderate to high dextrose	4 mg/kg/min or 12–12.5 g/hour	1.0–1.6
Carbohydrate controlled 4–6 mg/kg/min		
Noncarbohydrate controlled 6–8 mg/kg/min		
Low dextrose ≤3 mg/kg/min	4 mg/kg/min or 12–12.5 g/hour	1.0–1.6
Low dextrose ≤3 mg/kg/min	No lipids	1.0–1.6

Dextrose and lipids are calculated based on variable infusion rate. Amino acids are calculated based on daily protein requirements or allowances. These solutions are designed to be infused in 4 hours but this is variable. *IDPN*, Intradialytic parenteral nutrition. *gram/kilogram per body weight.

TABLE 35.2 Composition of IDPN Solution

IDPN Composition	Minimal Amount	Maximal Amount	Average
Amino acids	40 g	112 g	66 g
Dextrose	3 mg/kg/min	8 mg/kg/min	6 mg/kg/min
Lipids	10%	20%	1.5 cal/mL
Calories	900 kcal	1400 kcal	1150 kcal
Fluid	500 mL	1000 mL	750 mL

IDPN, Intradialytic parenteral nutrition.

Limitations of Clinical Trials of Intradialytic Parenteral Nutrition Therapy

The experimental design of nearly all studies conducted on IDPN has limitations. These include inadequate statistical power due to limited sample size, absence of control groups, lack of rigorous description, use of inclusion, and exclusion criteria to select patients with PEW. The dose of dialysis that patients received in the studies was not standardized and was not described. The length of IDPN therapy was not of adequate duration to draw firm conclusions regarding the effectiveness of IDPN. Follow-up periods were often brief. The intake of oral nutritional supplements or the intake of food was not standardized and was not well described. Due to these limitations, concrete conclusions regarding the effectiveness of IDPN cannot be drawn.

Nonrandomized Studies of Intradialytic Parenteral Nutrition

Key nonrandomized studies are presented in Table 35.5. In 1975, Heidland and Kult published the first report describing the use of IDPN therapy during a 60-week study period in 18 patients receiving maintenance hemodialysis three times a week. Patients were given 16.7 g of essential amino acids, including histidine, and 250 mL of a mixture of D/L-malic acid, xylitol, and sorbitol during the last one-half hour of hemodialysis. During the first 3 months, some nonessential amino acids were added to the IDPN. After 16 weeks of IDPN therapy, 13 patients were discontinued out of the 18 patients. With every hemodialysis session, about 100 g of protein was also included. The food intake was not constant. After 30 weeks of IDPN therapy, serum albumin and serum total protein levels were reported to increase significantly. Serum transferrin level, complement level, and hemoglobin level decreased. In a study by Piriano of 21 MHD patients who had lost at least 10% of their dry weight, 16 were treated with one type of IDPN mixture for 20 weeks. IDPN was given to these 16 patients who had 400 mL of 50% glucose and 400 mL of 8.5% essential amino acids and nonessential amino acids. Five out of 21 patients who had lost at least 15% of their dry weight were treated with a solution mix of 50% glucose and essential amino acids. The dialysis dose, the volume of IDPN,

TABLE 35.3 Content of Selected Nutrients in Some Currently Available Oral Nutritional Formulations

	Total Carbohydrates (g)	Total Protein (g)	Total Fat (g)	Total Calories (kcal)	kcal/mL
Nepro (240 mL)	39.4	19.1	22.7	425	1.8
Nepro (1000 mL)	166.8	81	96	1800	1.8
Boost glucose control (237 mL)	20	14	12	250	1.06
Boost glucose control (1000 mL)	84	58.2	49.4	1060	1.06
Boost (240 mL)	41	10	4	240	1.0

TABLE 35.4 Commonly Used Modular Products

Product	Amount	kcal	CHO* (g)	PRO† (g)	Fat (g)	Na (mg)	K	P (mg)	Ca (mg)	Adds
LiquaCel Sugar Free	1 oz	90	9	16	0	30	10	NA	0	Protein
MCT‡ oil	1 mL	7.7	–	–	–	–		–	–	Fat
NutraPro	26 g	80	2	16	1	NA	NA	NA	NA	Protein
ProMod	1 oz	100	14	10	0.6	55	20	95	–	Pro/kcal
ProStat Sugar Free	1 oz	100	10	15	0	50	20	50	–	Protein
Proteinex 2Go	2.5 oz	100	0	26	0	50	25	NA	NA	Protein
Proteinex 15	1 oz	60	0	15	0	6	9	2	–	Protein
Proteinex 18	1 oz	72	0	18	0	6	9	2	–	Protein
Proteinex 100	1 oz	100	7	18	0	6	9	2	NA	Protein
Resource Beneprotein	1 scoop	25	0	6	0	15	30	NA	20	Protein
Whey Protein ProCel	1 scoop	28	<1	5	<0.5	10	35	27	40	Protein

**CHO*, carbohydrate; †*PRO*, protein; ‡*MCT*, medium-chain triglyceride.

and the comorbid conditions of these MHD patients were not well described. Neither of these groups gained weight, and neither of these groups had any significant increase in serum albumin level. The only exception is that patients who received essential and nonessential amino acids, which did not have hyperparathyroidism gained weight.

Bilbrey et al. reported that in 47 MHD patients with severe PEW who received IDPN for 3 months, there was a significant increase in serum albumin levels (mean ± SD, from 3.30 ± 0.38 g/dL to 3.71 ± 0.30 g/dL, $p < 0.001$) and serum transferrin levels (mean ± SD, from 165 ± 37 to 200 g/dL ± 62 mg/dL, $p < 0.001$) in survivors. There was no increase in serum albumin or serum transferrin levels in the nonsurvivors. The dialysis dose, comorbid conditions, and duration of therapy of IDPN were not reported. Capelli et al. reported in their retrospective study of 81 MHD patients a survival difference between 50 patients who received IDPN and 31 patients who did not. In those patients treated with IDPN, the body weight was 10% less than their desirable body weight and/or who had at a minimum 10% weight loss. All patients in the study had reduced serum albumin levels. In the 31 patients comprising the control group, a history of recent weight loss or low body weight was not consistently present. All the patients in the study group received oral nutritional supplements and/or nutritional counseling at the initiation of the study. In those patients who did not respond to this supplementation of nutrition, IDPN was started. The IDPN solution had a 10% to 20% lipid emulsion (20–500 kcal/dialysis session), variable amounts of D-glucose based on the presence or absence of diabetes, and 50 g of essential amino acids. Mortality rate was 36% in the IDPN-treated patients ($p > 0.05$) and 48% in the control group. The time to death was significantly greater (mean ± SD, 16.9 ± 7.9 versus 7.5 ± 4.2 months; $p < 0.001$) in the nonsurvivors in the IDPN-treated patients. A nonrandomized study reported by Foulks et al. had 72 patients with PEW who failed to respond to dietary counseling who received IDPN. If there was a 10% increase in dry body weight or an increase in serum albumin of ≥0.5 g/dL, these patients were stratified as responders while they received IDPN. In these responders, mortality was significantly lower. The responders had a significantly lower serum albumin levels compared to nonresponders (mean ± SD, 2.2 ± 0.7 versus 3.0 ± 0.8 g/dL; $p < 0.0001$). Both the responders and nonresponders had similar body weights both before and after treatment with IDPN. Responders had higher hospitalization rates during the 6 months prior to the initiation of IDPN ($p < 0.0001$), but during IDPN therapy, only 52% of responders were hospitalized as compared to 76% of nonresponders ($p < 0.0001$). Only the responders had significantly reduced hospitalization rates. It is a plausible hypothesis that the nonresponders' increased morbidity reduced their ability to respond to IDPN therapy. It is also conceivable that the improved clinical course of the responders was due to IDPN.

A retrospective study compared 22,517 control MHD patients with 1679 MHD patients who received IDPN. In the 1679 patients who received IDPN, the composition of IDPN was not identical. There was a significant decline in the odds ratio of death at 1 year in those patients with serum albumin levels of ≤3.3 g/dL treated with IDPN after correction for case mix and predialysis serum creatinine

TABLE 35.5 Nonrandomized Trials of IDPN

Study	Design	Treatment Duration	No. w/ PEW	Parameters Measured	Outcome
Heidland and Kult, 1975	18 pts; 16.75 g EAA, 100 kcal; no control	60 weeks	Most did not	Alb, total protein, complement levels, transferrin	Increase in Alb, total protein, transferrin, complement levels after 16 weeks therapy in 13 pts. When therapy was discontinued for 6 weeks, decrease in complement levels, transferrin.
Piriano, 1981	16 pts: 16.5 g EAA + 1 NEAA, 200 g glucose 5 pts: 10.2 g glucose/EAA only	20 weeks	5 (in EAA group lost >15% of usual BW)	BW	In the EAA + NEAA group, 8 pts gained >10% BW; the other 8 lost weight. Pts in the EAA group gained weight if they did not have an acute illness.
Powers, 1989	18 pts; 250 mL 50% glucose, 250 mL RenAmin*	46–165 infusions	All	Weight gain, Alb, TSF, MAMC	Weight gain (12.6 ± 4.9 lb) in 11 of 18 pts. No change in Alb.
Bilbrey, 1989	20 pts; 50 g EAA + NEAA, 50 g lipids, 125 g glucose	90 days minimum	All	BW, MAMC	Only MAMC improved.
Matthys, 1991	10 pts; 16.75 g EAA	3 months	All	Quality of life, Hct, BW, degree of edema	BW increased starting from the first month of therapy ($p < 0.01$). Scoring index of general condition increased ($p < 0.01$).
Bilbrey, 1993	47 pts; 400 mL 15% AA, 150 mL 70% glucose, 250 mL 20% lipids	90 days minimum	All	Alb, transferrin, mortality	29 survived, 18 died. Survivors had an increase in Alb and transferrin. No data on cause of death, dialysis dose.
Chertow, 1994	1679 pts: 1.2 g protein/kg, 15 kcal/kg 22,517 pts: no IDPN	12 months or until death		Alb, URR, odds of death	Decrease in mortality in IDPN-treated pts who had Alb ≤3.3 g/dL.
Capelli, 1994	50 pts: 50 g EAA, 50 g lipids, 125 g glucose, dietary suppl (discontinued once IDPN started) 31 pts: dietary suppl	9 months	All had Alb <3.5 g/dL, BW <90% of desirable BW, or BW loss >10% over 2 months	Alb, BW, mortality	32 of 50 treated pts and 16 of 31 untreated pts survived. Weight gain in treated survivors; no weight gain in survivors who were untreated. No weight gain in nonsurvivors in either group. 6 months of IDPN before change in weight or Alb.

Continued

Table 35.5 Nonrandomized Trials of IDPN—cont'd

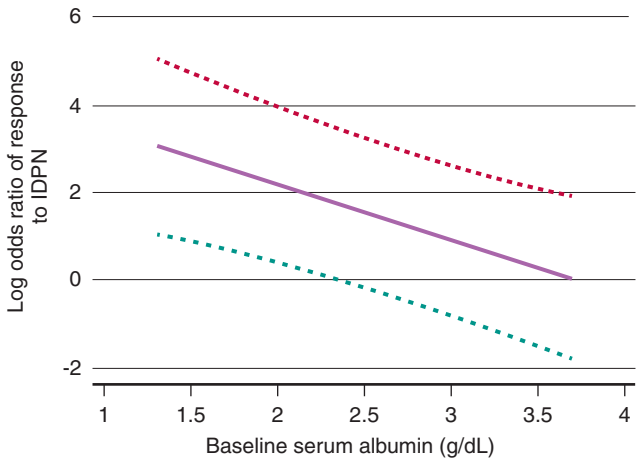
Study	Design	Treatment Duration	No. w/ PEW	Parameters Measured	Outcome
Foulks, 1994	72 pts; 0.64 g N/kg, 3.78 kcal/kg as lipids, glucose	Mean of 159 days in responders, 222 days in nonresponders		Mortality, hospitalization rate	Decreased mortality and hospitalization rate in responders.
Smolle, 1995	16 pts; 0.8 g/kg EAA + NEAA	16 weeks		Alb, skin test reactivity, WBC, SCr	NA
Cranford, 1998	43 pts; 63 g EAA + NEAA, 18.4 g lipids, 92.5 g carbohydrates	6 mos		Alb, BUN, hospitalizations	NA
Hiroshige, 1998	10 pts: 200 mL 50% glucose, 200 mL 7% EAA, 200 mL 20% lipids 18 pts: dietary counseling	12 months	All	BW, BMI, TSF, MAMC, Alb, transferrin, plasma AA profile, mortality	All IDPN-treated pts survived; five pts without IDPN therapy died (three due to sepsis, one due to GI bleeding) during the study period.
Mortelmans, 1999	26 pts (16 pts completed study, 10 pts withdrew); 250 mL 50% glucose, 250 mL 20% lipids, 250 mL 7% AA	9 months	All	BW, MAMC, lean body mass, transferrin, serum preAlb levels	BW increased ($p < 0.05$); transferrin, PA increased. TSF increased ($p < 0.05$). No such change in pts who withdrew.
Blondin, 1999	45 pts[†]	6 months	All had mean Alb <3.2 ± 0.4 g/dL	Alb, BUN, morbidity, URR, hospitalization rate	Decrease in hospitalization rate ($p < 0.05$), increase in Alb ($p < 0.05$).
Cherry, 2002	24 pts; 250 or 500 mL 10% AA, 250 mL 50% glucose, 250 mL 20% fat emulsion	4.3 months (mean)	All	Alb, dry BW	Increase in dry BW, Alb.
Dezfuli,2009	196 pts. IDPN No control group	3–12 months	All	Serum albumin	72% of patients had increase in serum albumin with a mean increase of 0.4 g/dL.

AA, Amino acid; *Alb*, albumin; *BMI*, body mass index; *BUN*, blood urea nitrogen; *BW*, body weight; *EAA*, essential amino acids; *GI*, gastrointestinal; *Hct*, hematocrit; *IDPN*, intradialytic parenteral nutrition; *MAMC*, mid-arm muscle circumference; *NA*, not applicable; *NEAA*, nonessential amino acid; *PA*, preserum albumin; *PEW*, protein-energy wasting; *pts*, patients; *SCr*, serum creatinine; *TSF*, triceps skinfold; *URR*, urea reduction ratio; *WBC*, white blood cell. *RenAmin, 6.5% parenteral solution; [†]45 patients failed the nutrition algorithm and met the operational definition of malnutrition.

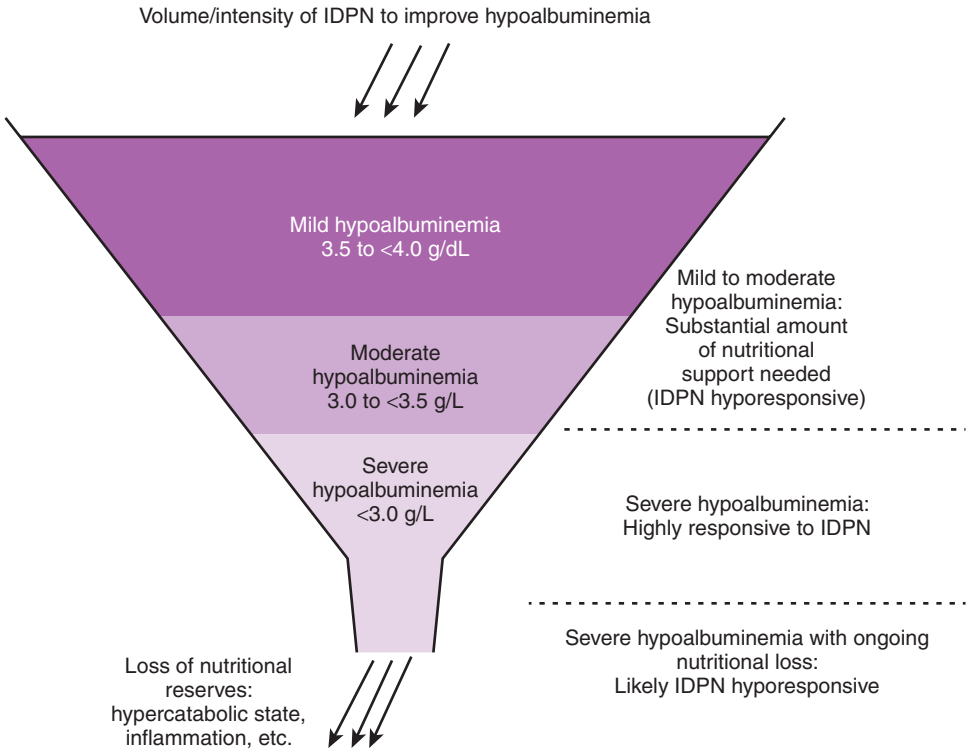
levels compared to patients who had comparable serum albumin levels who did not receive IDPN therapy. In patients treated with IDPN who had serum albumin levels of ≥3.5 g/dL at 1 year, the mortality was higher. In the MHD patients who had a predialysis serum creatinine level of 8.0 mg/dL or lower, the survival effect of IDPN was higher.

Hiroshige et al., in a nonrandomized study, published the results of IDPN therapy in 10 MHD patients. The control group included 18 MHD patients who refused IDPN therapy and were given dietary counseling. The treated group received IDPN for 12 months and consisted of 200 mL of 50% glucose, 200 mL of 20% lipid emulsion, and 200 mL of 7.1% essential amino acids per dialysis session. The baseline nutritional measures between the two groups did not differ significantly. In the treated group, during the IDPN therapy, there was a significant rise in serum albumin and transferrin, triceps skinfold thickness, body weight, and mid-arm muscle circumference. The control group patients showed measurable and significant differences in these parameters. A reduction in plasma essential amino acids was seen in the control group over the duration of the study.

Dezfuli et al., in a prospective cohort of 196 MHD patients with reduced serum albumin levels, examined the predictors of response to IDPN in a multivariate logistic regression model (Figs. 35.2 and 35.3). Patients with severe hypoalbuminemia, defined as a baseline serum albumin level of less than 3.0 g/dL, totaled 134. The average ± SD period of IDPN therapy was 5.8 ± 2.4 months. The baseline level of serum albumin was lower in MHD patients who responded to IDPN (mean ± SD, 2.68 ± 0.47 g/dL). A multivariate logistic regression analysis adjusted the associations for age, gender, diabetes, and IDPN time. The presence of severe hypoalbuminemia (serum albumin, 3.0 g/dL) at baseline was associated with a 2.5 times higher chance of responding to IDPN (95% confidence interval, 1.3 to 4.9; p = 0.006). The same severe hypoalbuminemia was associated with a 3.5 times increased likelihood of serum albumin correction by at least 0.5 g/dL (95% confidence interval, 1.8 to 6.8; p = 0.001). The authors concluded that the degree of response to IDPN correlated with the severity of hypoalbuminemia.



• **Fig. 35.2** Association of serum albumin at baseline to odds ratio of response to IDPN adjusted for patient demographics and length of treatment based on cubic spline analysis. *Solid line* is odds ratio, *dotted line* is 95% confidence interval. *IDPN*, Intradialytic parenteral nutrition.



• **Fig. 35.3** Hypothetical model to explain the association between the degree of response to IDPN with severity of hypoalbuminemia. *IDPN*, Intradialytic parenteral nutrition.

Randomized Prospective Controlled Trials of Intradialytic Parenteral Nutrition

Key randomized trials on IDPN are presented in Table 35.6. Over 12 weeks, Cano et al. studied 26 MHD patients with PEW. The IDPN-treated group consisted of 12 patients, and the rest were in the control group. The treated group exhibited a significant rise in body weight and serum transthyretin (prealbumin) and serum albumin levels. There were also increases in mid-arm muscle circumference, skin test reactivity, plasma apolipoprotein A1, and plasma leucine levels. None of the control patients experienced a rise in any of these parameters. Of note, the IDPN-treated group had a statistically nonsignificant lower baseline value of many of these measures. This may or may not have predisposed them to increases of these measures during therapy with IDPN. The plasma lipid levels did not change, but the plasma apolipoprotein A1 levels increased. The IDPN therapy provided an estimated 1.6 g/kg body weight of fat and 0.08 g/kg of nitrogen from essential and nonessential amino acids.

In a study by Toigo et al., 18 MHD patients were assigned in a random fashion to three IDPN treatment regimens. These regimens differed according to the amino acid content of the solutions. In these 18 patients, most had PEW. Patients received either only essential amino acids or a combination of nonessential and essential amino acids or an amino acid–free solution with an isocaloric infusion of 5% glucose. All three IDPN regimens contained vitamins, minerals, and trace elements. IDPN was given three times weekly for 2 months. The only change experienced in the three groups was that the patients who received only essential amino acids had gains of body weight. Twenty-one patients on MHD were randomly assigned to receive IDPN

TABLE 35.6 Randomized Prospective Trials in IDPN

Study	Design	Treatment Duration	No. w/PEW	Parameters Measured	Outcome
Wolfson, 1982	8 pts. EAA + NEAA + glucose solution versus normal saline	NA	NA	Plasma amino acid levels	Unclear if plasma amino acid levels increased.
Toigo, 1989	11 pts: 26.5 g modified EAA 10 pts: 24 g EAA + NEAA	6 months	None	Nerve conduction velocity, Alb	Decrease in Alb in the EAA + NEAA group.
Cano, 1990	12 pts: 0.08 g N/kg (per HD session) from EAA + NEAA, 1.6 g/kg (per HD session) lipids 14 pts: no intervention	3 months	All	BW, appetite, MAMC	Increase in calorie (9 kcal/kg/day) and protein intake (0.25 g/kg/day) in IDPN-treated pts.
McCann, 1999	19 pts; 70% glucose, 15% amino acids, 20% lipids	11 weeks	NA	Delivered Kt/v, URR	Reduction in delivered Kt/V in pts who received amino acid–containing IDPN
Navarro, 2000	17 pts	3 months	NA		Positive net balance of amino acids. Increase in PCR, Alb, transferrin.
Cano, 2006	17 pts: olive oil–based IV lipid emulsion 18 pts: soybean oil–based IV lipid emulsion	5 weeks	NA		Both groups showed similar improvement in nutritional status, plasma lipid, oxidative, and inflammatory parameters.
Cano, 2007	89 pts: IDPN 93 pts: control	12 months	All	Primary end point, all-cause mortality; secondary endpoints, hospitalization rate, BW, Karnofsky score, BMI	No difference in hospitalization rate or mortality between 2 groups.

Only clinical trials with eight patients or more are listed. *Alb*, Albumin; *BMI*, body mass index; *BW*, body weight; *EAA*, essential amino acid; *HD*, hemodialysis; *IDPN*, intradialytic parenteral nutrition; *IV*, intravenous; *MAMC*, mid-arm muscle circumference; *NA*, not available; *NEAA*, nonessential amino acids; *PCR*, protein catabolic rate; *PEW*, protein-energy wasting; *pts*, patients, *URR*, urea reduction ratio.

therapy for 6 months. Ten patients were given a combination of nonessential, and essential amino acids and 11 patients were given only essential amino acids as the nitrogen source. Baseline energy input before the initiation of IDPN was low, and at baseline, the mean serum albumin level was normal. Protein intake and mean baseline body weight were decreased but not significantly. With the essential and nonessential amino acid acids, there was a reduction in serum albumin levels and an increase in normalized protein nitrogen appearance.

The French Interdialytic Nutrition Evaluation Study (FineS) is, to date, the largest prospective randomized study to examine the benefit of IDPN in dialysis patients. A total of 186 MHD patients aged 18–80 years undergoing dialysis for at least 6 months were randomly assigned to receive IDPN therapy (n = 93) or not receive therapy with IDPN (n = 93). The treatment period was 1 year, and IDPN was given during three times a week dialysis. All patients, i.e., both the IDPN-treated group and the control group, received oral nutritional supplementation. All patients in the study had PEW, defined as having at least two of the following: (1) BMI of <20 kg/m^2; (2) serum albumin <3.5 g/dL; (3) edema-free weight loss of greater than 10% over the previous 6 months; and (4) serum transthyretin levels <30 mg/dL. The exclusion criteria were (1) total parenteral nutrition (TPN) received within the 3 months preceding the study; (2) single pool Kt/V <1.2; (3) less than 12 hours of dialysis treatment per week; (4) presence of severe comorbid conditions that adversely affect 1-year survival; (5) fasting serum triglyceride levels >300 mg/dL; and (6) hospitalization at the time of randomization. The follow-up period was 2 years. Energy and nutritional intakes were monitored at baseline and at 3, 6, 12, 18, and 24 months. The IDPN therapy in this study provided at months 3, 6, and 12 equivalents of 6.6 ± 2.2, 6.4 ± 2.1, and 6.1 ± 2.2 kcal/kg (mean ± SD) of amino acids. To estimate the time-averaged dose given daily, one should multiply these estimates by 3 (three sessions of hemodialysis per week) and then divide by 7 (the number of days per week). At months 3, 6, and 12, oral supplements provided 5.9 ± 2.7 kcal/kg/day and 0.39 ± 0.18, 0.38 ± 0.18, and 0.37 ± 0.18 protein/kg/day. There was patient-to-patient variability as well as variability among hemodialysis centers with regard to the intake of nutrients from the IDPN and spontaneous intake. There was no statistically significant difference in mortality, hospitalization rates, and indices of PEW between the IDPN-treated group and the control group. The Karnofsky scores did not change from baseline in either the control group or the group that received IDPN. Both groups received oral nutritional supplements, and this may have played a role in the failure to demonstrate any difference in outcomes between the groups. Of note, the patients in the IDPN-treated group who had a rise in serum transthyretin of greater than 30 mg/L within the first 3 months of the study showed an approximately 50% reduction in mortality in 2 years. The authors note that although this is the largest prospective randomized trial to date, it was still underpowered.

Indications for Initiation of Intradialytic Parenteral Nutrition

The first step in the management of a patient with PEW is to explore reversible causes, and if none are found, intensive nutrition counseling with oral supplements (enteral support) should be attempted. An enteral feeding using the gastrointestinal (GI) tract to deliver all or part of a person's nutrient requirements, including an oral diet, the use of liquid nutrients, or delivery of part or all the daily requirements via tube (nasogastric tube or percutaneous endoscopic gastrostomy [PEG] tube), should be attempted prior to parenteral feeding. Studies show positive results when patients consistently consume estimated nutrient needs either via oral intake or by tube feeding. Many patients do not consent for a PEG tube, and a nasogastric tube is a very temporary solution. When sustained use of oral nutritional supplements fails to improve nutritional status, a trial of IDPN can be attempted.

General criteria for initiation of IDPN/intraperitoneal nutrition (IPN) includes:

- Minimum of 1 month of intense nutrition counseling (emphasizing the need for increased protein and/or kcalories)
- Minimum 1–2-month trial of oral supplementation with no evidence of improvement
- Continued protein malnutrition as evidenced by:
  - Three-month average s-albumin <3.5 g/dL (BCG)
  - Progressive 3-month decline in s-albumin <3.5 g/dL bromocresol green (BCG)
  - Normalized protein nitrogen appearance (nPNA) <0.8 g/kg/day or documented protein intake of less than the recommended level

  and/or
- Continued energy malnutrition as evidenced by:
  - Edema-free body weight $<90\%$ of ideal weight
  - BMI <18
  - Weight loss $>5\%$ over 3 months
  - Weight loss $>10\%$ over 6 months
  - Weight loss 20%, no timeframe

  Variation in criteria is common.

IDPN/IPN can be discontinued if the s-albumin is maintained >3.8 g/dL for more than 3 consecutive months. With regard to decision making with multiple feeding routes, it is not uncommon for a patient to receive IDPN in addition to an enteral tube feeding, and this is a viable option as these are two separate feeding routes that can successfully aid in complimenting a patient's nutritional status as volume may be a limiting factor with an enteral tube feeding. However, it is important to note that TPN and IDPN cannot be utilized simultaneously as the billing code is the same and only "one therapy" will be paid for, thus leaving the patient responsible for the cost of one of the feeding therapies. Often, as a patient is weaned off TPN, it is desirable to start IDPN in the process, although it is important to ensure that the therapies do not overlap.

Composition of Intradialytic Parenteral Nutrition

Care should be taken to infuse IDPN in a low volume, to increase it incrementally, and keep the IDPN infusion rate to less than 300 mL/hour but not to exceed a maximum infusion rate of 350 mL/hour, dependent on the substrates administered in the duration of the infusion.

Amino Acids

The amino acid formulation contains essential and nonessential amino acids, and the initiation should be 1.0 to 1.2 g/kg dependent on comprehensive assessment of the patient. It is suggested to avoid protein restriction in patients with liver failure, using the same recommendations utilized for other critically ill patients and using the patient's usual weight rather than the actual weight in predictive equations due to complications associated with ascites, edema, portal hypertension, and hypoalbuminemia. Amino acids can be delivered in doses as high as 1.8 g/kg or potentially higher depending on the patient's lean body mass catabolism.

The amino acid's impact on volume is dependent on its concentration. For example, 100 g of protein in 10%, 15%, or 20% is 1000 mL, 667 mL, or 500 mL, respectively. Thus, a 20% amino acid solution has the least volume, and in the CKD population, which is sensitive to volume management, this is of utmost importance. Of note, the 10% amino acid solution has the lowest osmolality, and in identifying patients with intolerance, this should be taken into consideration. A two-in-one solution with amino acid and dextrose is administered over a 2-week titration schedule, with 50% of the dose administered during week 1 and achieving the goal rate by week 2 in order to assess tolerance to the infusion.

Dextrose

In patients with diabetes mellitus, particularly patients with a history of uncontrolled hyperglycemia and insulin resistance, glycemic control is a potential challenge. Dextrose load may cause or aggravate hyperglycemia, and the dextrose utilization rate should not exceed 4–6 mg/kg/min for patients with diabetes and should not exceed 8 mg/kg/min for patients who are nondiabetic. The amount of dextrose utilized in each IDPN bag has substantially decreased from the historically high energy composition consisting of approximately 125 g and greater to as low as 20 g, and the amount of dextrose utilized is dependent on the number of additional substrates (amino acids/lipids) and infusion time overall, in addition to whether the patient is diabetic. Keep in mind that if lipids are added to the IDPN, the dextrose necessary for solution stability will be impacted; this will be further discussed. Patients with diabetes may have specific considerations:

- Blood glucose should be checked from the arterial line or by use of a peripheral stick (finger stick) prior to initiation of IDPN, and at the beginning, an hour into the infusion and at the end of IDPN administration during the first week of dialysis and once a week thereafter until it is determined that blood glucose remains stable.
- Patients may require adjustments to the insulin regimen dependent on the blood glucose levels and the amount of dextrose provided. Insulin is not delivered in IDPN bags, although some companies may send insulin to be added to the IDPN bag immediately prior to infusion. Insulin added to the bag may pose a concern in the identification of an exact dosage of insulin delivered in the event a patient does not complete an infusion.
    - Endogenous insulin released in response to IDPN can induce postinfusion reactive hypoglycemia due to delay in action of endogenous insulin. About 30 minutes to 45 minutes before the end of a dialysis session, IDPN can be completed, which allows time to monitor for reactive (rebound) hypoglycemia. Within 30 minutes prior to the end of the infusion, if the patient is capable of oral intake, they should consume a snack to aid in the prevention of hypoglycemia. A postinfusion snack should consist of 15–30 g carbohydrates. Examples of 15-g carbohydrate sources are 15 grapes, one-half sandwich, 4 oz fruit cup, six to eight crackers, one cup raspberries, and a small apple or pear.

A low-carbohydrate IDPN formulation is available from commercial IDPN companies.

Lipids

IDPN formulations are tailored to a patient's energy and protein needs, higher or lower dextrose, specific protein levels, and the inclusion or exclusion of lipids. Lipids are contraindicated if a patient presents with an egg or soy allergy due to the egg yolk phospholipids and soybean oil within the fat emulsion. Additional contraindications may include a serum triglyceride level of >400 mg/dL, as this may suggest poor lipid clearance. Typically, a patient's caloric needs and requirements for lipids can be met through oral intake and/or use of EN, although the addition of lipids provides an additional energy source if intense nutritional counseling does not promote optimized caloric intake. Lipids can be added as a three-in-one solution by the seventh treatment if lipids are utilized, and a test dose is recommended with a 30-minute initial infusion. A three-in-one solution or intravenous fat emulsion (IVFE)–containing IDPN will require increased dextrose for solution stability. The three-in-one solution has a higher volume; thus, patient weight and treatment time need to be taken into consideration. The serum lipid clearance rate is dependent upon infusion dose and time and should not exceed 4 mg/kg/min.

Symptoms such as nausea and vomiting associated with hypertriglyceridemia can be reduced if the maximum infusion rate is less than 250 cc/hour. In the FineS study, reducing the infusion rate by 50% (125 cc/hour) resulted in a resolution of nausea and vomiting. After a 2-week period, the infusion rate was increased to 250 cc/hour, with no recurrence of symptoms. Reduction of the infusion rate can partially correct the

development of hypertriglyceridemia. It is prudent to measure serum lipids and liver function tests initially at the onset of therapy and potentially quarterly, though development of fatty liver associated with IDPN is rare.

Until recently, the majority of the commercial IDPN companies have utilized Intralipid (20% fat emulsion, 100% soybean), although great interest has been placed on SMOFlipid, which is a 20% fat emulsion containing 30% soybean oil, 30% medium-chain triglycerides (MCT), 25% olive oil, and 15% fish oil, and more recently on Clinolipid (80% olive oil, 20% soybean oil), which is now available in the United States and implemented due to its anti-inflammatory and antioxidant effects. Tables 35.1 and 35.2 show the infusion rates and the composition of IDPN, respectively.

Additives

Electrolytes are generally not added to IDPN as dialysis patients are prone to electrolyte imbalances, although electrolytes may be added if warranted. Calcium, sodium, potassium, phosphate, and magnesium can be added to the IDPN during compounding. Prior to the addition of additives, a review of biochemical parameters between the physician and pharmacy occurs to ensure that no medication interactions affecting electrolytes are impacting outcomes and to suggest an appropriate and safe dose that is dependent on the IDPN formulation.

An example would be in assessing a patient who has chronically low phosphorus for the addition of phosphorus additive: ensure that the patient's diet has been liberalized to allow for foods containing phosphorus, hold phosphate binder medications, consider use of an oral phosphorus supplementation, although this is not necessary, and monitor the trend to identify if the phosphorus level does or does not improve. If phosphorus remains below established normal levels, then a phosphorus additive may be considered and may be utilized either in the form of sodium phosphate or potassium phosphate, dependent on the remaining biochemical parameters.

Vitamins and trace elements are not added routinely to IDPN as the micronutrients may be lost in the dialysate during ultrafiltration, although these are available for patients who do not tolerate oral vitamin supplementation. Historically, it has been documented that vitamins and trace elements are added to IDPN during the last 30 minutes, although this is variably dependent on the brand utilized by specific companies compounding IDPN and in some instances may be added immediately prior to the administration of IDPN in the dialysis facility.

Infusion and Monitoring of Intradialytic Parenteral Nutrition Therapy

Initiation of IDPN varies whether the therapy is a two-in-one or a three-in-one therapy and is customized to specific patient needs. General administration is 50% of the volume of the amino acid and dextrose on the first three treatments (week 1) and progresses to the full volume on the second three treatments (week 2). If lipids are to be utilized, they are introduced on the seventh treatment (week 3), with the full volume of amino acid and dextrose following a 30-minute test dose to determine a lipid intolerance or anaphylactic reaction to the lipid (flu-like symptoms, skin rash, temperature spike, or nausea).

To prevent "cold shock," the solution must be at room temperature prior to infusion. Solutions may be removed up to 24 hours in advance but at least 4 hours prior to infusion. The infusion is started shortly after dialysis is initiated and terminated 15–30 minutes prior to the end of therapy, enabling provision of intravenous (IV) medications, and this can vary per patient. Dependent on clinical preference, IV medication administration can be completed pre or post infusion. IDPN is not compatible with ESAs, vitamin D analogues, IV iron therapies, and the antibiotic Daptomycin. In addition, IDPN is not compatible with sodium thiosulfate (STS); thus, knowledge of a patient being treated with STS in advance is necessary to appropriately adjust the infusion time for IDPN to accommodate STS therapy.

Intolerance is generally easy to remedy based on early identification and action. Often, as noted, a reduction in the infusion rate is a substantial remedy. Other potential remedies include ensuring that the IDPN formula is at the correct temperature, reduction of the volume with incremental titration, reduction of the osmolality, and removal of lipids. A review of Na, Phos, K+, blood urea nitrogen (BUN), Kt/V, BS, A1c, Mg, weight, PO intake, and volume management is relevant in determining the underlying conditions that may be impacting a patient's intolerance to IDPN.

The frequency and parameters of monitoring the patient on IDPN depend on the specific patient and their metabolic condition in addition to their comorbidities. The company providing IDPN typically provides both monitoring and administration guidelines. Anthropometric and biochemical data typically monitored in the dialysis facility are generally sufficient to monitor the effectiveness of therapy, and due to the supplemental nature of IDPN, it is not necessary to gradually wean the patient off therapy. Based on the goals of therapy, patients may have IDPN discontinued when s-albumin is maintained >3.8 g/dL for more than three consecutive months.

Formulation Changes

Reviewing IDPN formulas for potential changes should be minimized during the first 3 months of therapy considering the half-life of albumin. Therefore, in months 2 to 3, it is reasonable, assuming the patient is in a steady state without stress, to monitor IDPN's impact on albumin. It is critical to review both albumin and weight trends, at the minimum, on a quarterly basis to identify the impact of IDPN therapy and to adjust the formulation to optimize nutritional outcomes. One should also assess and observe trends with

correction of protein status in uremic toxins (observe kinetics, intact parathyroid hormone (iPTH), etc.), acidosis, A1c, and additional comorbid factors. Companies that provide IDPN/IPN will aid in formulating the adjustments to ensure a safe formulation based on weight, patient status, and infusion time.

Factors that warrant potential formulation changes are as follows:

- Failure to respond to therapy, not related to minor stress/comorbid factors
- Evidence of a downward trend of albumin; decreasing in two of the previous three months
- Albumin < 3.5 g/dL, with no improvement from one of the past three months of therapy
- Patient exhibiting major stress; examples include nonhealing wounds, major surgery, cancer, chemotherapy or radiation therapy, or diseases associated with significant malabsorption
- Weight loss necessitating additional kcalories—addition of lipids
- Change in modality or treatment time (necessitates immediate change)
- Intolerance to formulation (necessitates immediate change)

Refeeding Syndrome

Refeeding syndrome in IDPN patients is extremely rare but can be serious. Following 72 hours of starvation, the energy source shifts from carbohydrate (CHO) to fat. Fat provides free fatty acid (FFA) substitutes for muscle, and ketoacids (from FFA) substitute for glucose in the brain, thus sparing protein from being utilized as the predominant energy source. The metabolic rate slows in response. There is a loss of intracellular ions: phosphorus, potassium, and magnesium, due to muscle catabolism.

Patients with the following have increased risk for refeeding syndrome:

- Anorexia nervosa
- Classic marasmus, kwashiorkor
- Residents admitted from skilled nursing facilities
- Unfed 7–10 days: evidence of stress/depletion
- Chronic disease, causing undernutrition
- History of alcohol intake
- Morbid obesity with massive weight loss

Once a malnourished patient is "refed," there are three primary factors surrounding the refeeding syndrome: a shift of predominant fuel source, a depletion of electrolyte stores, and protein anabolism with insulin release. This is often referred to as "flipping a light switch." The fuel shifts back from fats in starvation mode to CHO as the primary fuel source. As a result, there is a tremendous need for phosphorus for adenosine triphosphate (ATP), and there is a demand for 2,3 diphosphoglycerate, the oxygen-carrying component of the red blood cell. A depletion of phosphorus, potassium, and magnesium typically occurs as these minerals are shifted back into the cell because as the patient receives IDPN, they are receiving amino acids and dextrose.

Protein anabolism requirements—for every gram of N_2 (protein):

- 0.8 g PO_4
- 2.7 mEq Cl-
- 3.1 mEq K+
- 3.5 mEq Na+

The most classic marker of refeeding syndrome is hypophosphatemia, in addition to hypokalemia and hypomagnesemia.

IDPN patients continue to maintain EN and often take in sufficient kcalories to prevent refeeding syndrome. Occasionally, a patient returns to the dialysis facility following a prolonged period of hospitalization and may exhibit refeeding syndrome upon initiation of IDPN therapy. A patient such as this or one who may fit in the previously identified list should initiate or resume IDPN by titrating therapy in increments over 2 to 3 weeks or a slower titration as tolerated, with the addition of additives if warranted. Adequate vitamins, minerals, and trace elements are required for repletion as they function as cofactors and enzyme components in metabolism.

Intradialytic Parenteral Nutrition and Kt/V

Literature addressing the impact of IDPN on Kt/V is limited and conflicting. There have been studies that have not observed a significant impact of IDPN on Kt/V; however, McCann's data from 1999 indicate differing results. Patients received IDPN regimens with varying amounts of amino acid, dextrose, and lipids. The amino acid–containing IDPN reduced the mean Kt/V by 18%–23%, although patients met the goal of 1.26. It was theorized in unpublished data that inadequate CHO resulted in catabolized protein generating urea. Unfortunately, McCann's study is the only comprehensive randomized crossover study of patients receiving IDPN reviewing Kt/V in over 20 years. Dialysis duration may be a factor in the results. In the Cano study, Kt/V did not change from the baseline of 1.7 ± 0.3, and it is important to note that all patients had treatment times > 4 hours. The longer treatment time allows for a slower IDPN infusion rate and potentially greater utilization for protein synthesis resulting in less amino acid for urea generation. Prospective studies controlling for dialysis prescription as well as composition are necessary.

Advantages and Disadvantages of Intradialytic Parenteral Nutrition

Nutrition is provided with IDPN independent of the patient's appetite, GI motility/function (for example, patients with diabetes mellitus may suffer from gastroparesis), or anorexia. Adherence to the patient or the patient's ability to consume a diet does not influence the nutritional intake as IDPN is given intravenously. As IDPN is given using the patient's vascular access that is used for hemodialysis, there is no need for an additional IV access. IDPN can be tailored

to a patient's individual needs, such as lipid free or low glucose. Fluid that is administered with IDPN can be removed during the same hemodialysis session. The labor involved with the administration of IDPN is not onerous and does not add a significant amount of burden to dialysis nurses. As IDPN is a consistent amount of protein and energy with each dialysis session to supplement the patient's oral and/or enteral intake, it replaces amino acid losses incurred during the dialysis session, thus improving protein synthesis, energy metabolism, and potential weight gain.

IDPN is more expensive than any of the available enteral or oral nutrition therapies, although it is less expensive than TPN. The limited nature of the supplementation that is provided by IDPN is usually not adequate if the spontaneous oral intake of the patient is not substantial enough to meet a large portion of the patient's nutrition demands. Spontaneous intake of the patient should be at least greater than 20 kcal and at least 0.8 g protein/kg of the ideal body weight per day. IDPN is of limited value if the patient's spontaneous intake is less than the calorie and protein intake. IDPN cannot be used as the sole source of nutrition. The time that a given patient is exposed to IV nutrition is only about 9–16 hours per week, as it is given only during dialysis. As IDPN bypasses the gut interaction of nutrients, it is not physiological and lacks the trophic effects of nutrition on the GI tract. In the United States, coverage for IDPN by a multitude of insurance companies is not uniform, and therefore, many patients are not covered. Reimbursement for IDPN is provided by Medicare Part D, Medicaid, and private health insurance and is dependent on the patient's specific plan. The cost of therapy is impacted by deductibles, copays, and coverage gaps (referred to as the "donut hole"). The criteria for Medicare Part D (outlined earlier) is discussed next.

General Criteria for Initiation of Intradialytic Parenteral Nutrition/Intraperitoneal Nutrition Includes:

- Minimum of 1 month of intense nutrition counseling (emphasizing the need for increased protein and/or kcalories)
- Minimum 1–2-month trial of oral supplementation with no evidence of improvement
- Continued protein malnutrition as evidenced by:
  - Three-month average s-albumin < 3.5 g/dL (BCG)
  - Progressive 3-month decline in s-albumin < 3.5 g/dL (BCG)
  - nPNA < 0.8 g/kg/day or documented protein intake of less than the recommended level

  and/or
- Continued energy malnutrition as evidenced by:
  - Edema-free body weight < 90% of ideal weight
  - BMI < 18
  - Weight loss > 5% over 3 months
  - Weight loss > 10% over 6 months
  - Weight loss > 20%, no timeframe

Beyond the cost, research has been variable, with support for IDPN based largely on expert opinion and editorial consensus. Serum hepatic proteins and body weight are affected by multiple factors other than nutrition that can skew interpretation of the patients' nutritional status and the effect of IDPN. Additionally, IDPN does not change or improve a patient's eating behavior, nor does it encourage improved healthy eating habits to promote long-term modification.

Home Therapies

Home Hemodialysis Intradialytic Parenteral Nutrition

For home hemodialysis (HHD) patients requiring IDPN, the general criteria are the same as coverage for HHD IDPN by a multitude of insurance companies, which is not uniform. Reimbursement for IDPN is provided by Medicare Part D, Medicaid, and private health insurance and is dependent on the patient's specific plan.

The HHD 2/1 and HHD 3/1 IDPN formulations are calculated to provide approximately 50% of the amino acids over a 5-day per week treatment versus the 3-day per week treatment.

An example may be a patient receiving a 2/1 IDPN prescription providing 90 g amino acids 3 days per week and will be transitioning to HHD. The patient may receive the HHD 2/1 IDPN providing 45 g amino acids 5 days per week, infusing for perhaps 2.0 hours, thus keeping in mind to reflect changes in treatment time as the patient transitions to HHD. IDPN solutions require refrigeration. Patients are provided with a refrigerator and educated on the proper storage and administration, often through both the company providing the therapy and the health care team caring for the patient.

If the HHD patient is receiving IDPN and warrants an increase in therapy, the increase is done cautiously by considering the patients' treatment time not to exceed substrate utilization rates.

Intraperitoneal Nutrition

Certain PD-specific etiologies should be looked for in patients on PD that increases risks of PEW, such as extraperitoneal sclerosis, delayed gastric emptying, and excessive protein loss due to high transport status. The general criteria for initiation of IDPN/IPN are the same.

Protein losses during PD exceed the losses that occur during hemodialysis. Most of the research on intraperitoneal amino acids (IPAAs) or IPN utilizes amino acids in place of dextrose as the osmotic gradient during PD. The amino acids serve a dual purpose: cleanse the blood of toxins and aid in fluid removal by acting as an osmotic agent and serving as a provision of protein, which sufficiently replaces the ~5–15 g amino acids lost per day through the peritoneal membrane. This substitution of amino acids for dextrose reduces the absorption of excess kcalories from the

dextrose-containing dialysate, which could potentially alleviate the adverse effects caused by hyperglycemia in patients with diabetes mellitus and hypertriglyceridemia.

A commercially available amino acid solution is available containing a mixture of nine essential and six nonessential amino acids that are added to a peritoneal dialysate solution. This is a 1.1% amino acid solution along with a reduction in glucose concentration. The components of a 1.1% Nutrineal solution are shown in Table 35.7; additionally, Table 35.8 illustrates overall a sample of IPN solutions as a comparison. The peritoneal dialysate is used for one or two peritoneal dialysate exchanges every day. The dwell times are increased typically from 4 to 6 hours to enhance uptake of about 80% of the amino acid content in the peritoneal dialysate. Nutrineal is not readily available in the United States.

Formulas and Administration

The amount of amino acids delivered in IPN varies from 10 to 120 g and is dependent on the patient's PD regimen. IPN can be incorporated into manual or cycler exchanges. The absorption of amino acids is variable, ranging from 80% to 90% in a 5–6-hour dwell time in a manual exchange to 40%–50% in a shorter dwell time (<2 hours) on a cycler, and absorption is dependent on peritoneal membrane permeability in either case. In continuous ambulatory peritoneal dialysis (CAPD), IPN replaces one or two manual exchanges, and in continuous cycling, peritoneal

TABLE 35.7 Composition of 1.1% Nutrineal

Essential Amino Acids		Nonessential Amino Acids	
L-Valine	1.39 g/L	Arginine	1.07 g/L
L-Leucine	1.02 g/L	Alanine	0.95 g/L
L-Isoleucine	0.85 g/L	Proline	0.59 g/L
L-Methionine	0.85 g/L	Glycine	0.51 g/L
L-Lysine	0.76 g/L	Serine	0.51 g/L
L-Histidine	0.71 g/L	Tyrosine	0.30 g/L
L-Threonine	0.65 g/L		
L-Phenylalanine	0.57 g/L		
L-Tryptophan	0.27 g/L		
Sodium	132 mEq/L	Chloride	105 mEq/L
Calcium	5 mg/L	Lactate	40 mEq/L
Magnesium	0.50 mEq/L		
Total amino acids	1.1%		
Osmolarity	365		
pH	6.7		

TABLE 35.8 IPN Solutions

	Content of IPN Solutions per 2 L			
	Dextrose g	Protein g	Osmotic Strength Equivalency	Characteristics/Use
1.5% dextrose plus 1.375% aa	30	27.5	425 mOsm/L ~ 2.5% dextrose	Add calories and protein, moderate ultrafiltration
1% aa	0	20	411–412 mOsm/L ~ 1.5% dextrose	No dextrose load; replacement of aa/protein losses, adequate ultrafiltration
1.5% aa	0	30	445 mOsm/L ~ 2.5% dextrose	No dextrose load; replacement of aa/protein losses, moderate ultrafiltration
2% aa	0	40	478 mOsm/L ~ 4.25% dextrose	No dextrose load; replacement of aa/protein losses, high ultrafiltration
Nutrineal* PD4 Baxter (1.1% aa) (64% essential, 36% nonessential)	0	22	356 mOsm/L ~ 1.5% dextrose	No dextrose load; meal or calorie source is recommended to maximize protein utilization and adequate ultrafiltration

aa, amino acid; *IPN*, intraperitoneal nutrition. *Nutrineal, 1.1% amino acid peritoneal dialysis solution.

dialysis (CCPD), IPN replaces one of the cycler bags and may potentially utilize an IPN manual daytime exchange. In CCPD, the IPN may be used as the dedicated last fill option, although if the patient is utilizing icodextrin, the IPN should be used as either the first or second fill as IPN has not been studied with icodextrin at this time.

- Extraneal: PD solution containing icodextrin is a starch-derived, water-soluble glucose polymer and is used as a single long dwelling (8–16 hour) exchange. The rate of absorption is much slower than dextrose. IPN is not a substitute for icodextrin and, thus, is used before or after icodextrin with consideration of the PD prescription and ultrafiltration needs and hydration status.

The amount of amino acids that are delivered is dependent on the bag size and strength of the solution being replaced. Ultimately, the strength of the amino acids must mimic that of the dextrose in the dialysis prescription rather than meet protein needs to deliver optimal ultrafiltration. The optimal dwell time depends on the patient's peritoneal transport rate. An optimal dwell range is estimated to be 4 to 8 hours. A prolonged dwell increases the risk that some of the delivered amino acids will cross back into the peritoneal cavity and be lost with waste-containing dialysate as drained. Amino acids are good osmotic agents providing approximately twice the osmotic load of glucose per gram; thus, the ultrafiltration is approximately 10% to 20% stronger than a 2.5% and 1.5% dianeal solution, respectively. IPN is compounded in a pharmacy using either Baxter or Fresenius low-calcium 1.5% dianeal bags with the addition of amino acids (typically 20% as this is a lower volume compared to 15% amino acids) to deliver the prescribed dose.

Patients utilize aseptic technique when handling the amino acid solutions as they would the dianeal bags, with the difference being the amino acid (IPN) bags are delivered from the pharmacy and kept refrigerated and, thus, removed a minimum of 6 hours in advance, not to exceed 24 hours prior to the exchange.

Additives

Electrolyte additives are available for IPN, such as calcium gluconate, magnesium sulfate, potassium chloride, and sodium lactate, which are most often used as a buffering agent. It is recommended that patients attempt oral intake through diet to correct abnormalities and/or an oral supplementation prior to utilizing an additive. Sodium or potassium phosphate is not available as an additive for IPN, as it is too great a risk that phosphate will interact with the calcium chloride and form calcium phosphate crystals.

Monitoring of Intraperitoneal Nutrition Therapy

Monitoring IPN is similar to that of the patient on IDPN: the frequency and parameters of monitoring the patient depend on the specific patient and their metabolic condition, in addition to their comorbidities, with the addition of ensuring that optimum ultrafiltration is achieved.

The addition of amino acids to the peritoneal dialysate increases protein synthesis and the plasma levels of several proteins and amino acids. It is prudent to prevent an excessive load of amino acids and protein from the combined intake of intraperitoneal and oral intake to avoid high serum urea nitrogen levels and metabolic acidosis. The effects of IPAA supplementation on the peritoneal membrane, protein loss, and cytokine production have not been rigorously studied in long-term clinical trials. The consensus is that patients handle oral and intraperitoneal calorie intake in similar fashion.

Advantages and Disadvantages of Intraperitoneal Nutrition

As with IDPN, the nutrition provided with IPN is independent of the patient's appetite, GI motility/function, or anorexia. Adherence to the patient or the patient's ability to consume diet does not influence the nutritional intake as IPN is given via performing an exchange; thus, there is no need for an additional IV access or feeding tube. However, the therapy is reliant on the patient's functioning PD catheter and adherence to peritoneal exchanges. IPN is tailored to the patient's PD prescription rather than protein needs. This may be limiting; however, it may reduce dialysate glucose concentration and kcalorie load and mimics the prescribed dialysate, possibly improving glycemic control and lipid profile. The amino acids in the exchange are provided in a consistent dose to promote increased levels of serum proteins and protein synthesis. There is a lack of fullness, as exhibited with consuming additional high-protein formulas.

IPN is more expensive than any of the available enteral or oral nutrition therapies, although it is less expensive than TPN. IPN cannot be used as the sole source of nutrition. In the United States, coverage for IPN by insurance companies is not uniform, and therefore, many patients are not covered. Reimbursement for IPN is provided by private health insurance and is dependent on the patient's specific plan. The cost of therapy is potentially impacted by deductibles and copays.

Beyond the cost, research has been variable, with support for IPN based largely on expert opinion and editorial consensus. Serum hepatic proteins and body weight are affected by multiple factors other than nutrition that can skew interpretation of the patients' nutritional status and the effect of IPN. There is documented research indicating a reduction in phosphorus and potassium levels with IPN, net gains of amino acids, increased risk of metabolic acidosis that could increase protein catabolism, and weight gain, although insignificant. As stated, the research is variable. Additionally, IPN does not change or improve a patient's eating behavior,

nor does it encourage improved healthy eating habits to promote long-term modification.

Additionally, IPN may pose an inconvenience to the patient as the patient will receive multiple deliveries of supplies per week vs one, and IPN must be delivered from the pharmacy that compounds it. The solution must be refrigerated, and the patient will be required to remove the solution in advance of the exchange. The company that provides the therapy provides a refrigerator; however, a patient will be required to "house" two storage supplies, and some patients may need to plan for this in advance.

Summary

In the absence of single indicators of nutritional indices, there is an uncertainty of when nutritional goals are achieved. As discussed, hepatic proteins are compromised by a plethora of confounding factors beyond sole response to nutritional intake. It is noted that improved albumin and transthyretin are associated with improvement in morbidity and mortality, although factors such as inflammation, comorbidities, volume management, and the dialysis process itself impact the synthesis of hepatic proteins. Because of this, patients with CKD pose challenges in meeting protein/energy needs and in addition with management of volume status. IDPN/IPN is not meant to fulfill all of a patient's nutritional needs but rather is supportive parenteral nutritional therapy and relies on patient adjunct oral/enteral nutrition to meet nutritional needs. Malnourished patients, when provided with a consistent, complete nutrition, will respond with improved nutritional parameters, increased stability, and enhanced quality of life. An astute health care team and consistent monitoring will ensure the success of the patient on IDPN/IPN therapy.

Suggested Reading

Blondin J, Ryan C. Nutritional status: a continuous quality improvement approach. *Am J Kidney Dis.* 1999;33(1):198–202.

This is a historically relevant paper on IDPN with a retrospective look at hemodialysis patients with malnutrition who were followed up in the process of continuous quality improvement, and the costs of IV supplies, hospitalizations, and morbidity were reviewed.

Cano NJM, Fouque D, Roth H, et al. Intradialytic parenteral nutrition does not improve survival in malnourished hemodialysis patients: a 2-year multicenter, prospective, Randomized Study. *J Am Soc Nephrol.* 2007;18(9):2583–2591.

In this randomized trial of 186 malnourished hemodialysis patients in France who received oral nutritional supplements with or without 1 year of IDPN, IDPN did not improve 2-year mortality or other outcomes, while both groups demonstrated improvement in BMI and serum albumin and prealbumin, and an improvement in prealbumin during nutritional therapy was associated with a decrease in morbidity and mortality in malnourished hemodialysis patients.

Capelli JP, Kushner H, Camiscioli TC, Chen S-M, Torres MA. Effect of intradialytic parenteral nutrition on mortality rates in end-stage renal disease care. *Am J Kidney Dis.* 1994;23(6):808–816.

In this study of 81 patients receiving thrice-weekly hemodialysis treatments who had either a low serum albumin or protein catabolic rate, 50 patients received IDPN and 31 patients did not. There was no difference in overall survival, while the nondiabetic treated patients had the lowest mortality rates.

Chertow GM, Ling J, Lew NL, Lazarus JM, Lowrie EG. The association of intradialytic Parenteral Nutrition Administration with survival in hemodialysis patients. *Am J Kidney Dis.* 1994;24(6):912–920.

In this classic large data analysis, among hemodialysis patients who had received IDPN during 1991, at lower levels of albumin ≤3.4 g/dL, treatment with IDPN was associated with a reduction in the odds of death at 1 year, an effect that became stronger at lower levels of creatinine ≤8.0 mg/dL, while treatment with IDPN in patients with normal albumin was associated with increased mortality.

Dezfuli A, Scholl D, Lindenfeld SM, Kovesdy CP, Kalantar-Zadeh K. Severity of hypoalbuminemia predicts response to intradialytic parenteral nutrition in hemodialysis patients. *J Ren Nutr.* 2009;19(4):291–297.

In this prospective cohort of 196 hypoalbuminemic hemodialysis patients who received IDPN, predictors of IDPN response were examined using multivariate logistic regression. The analyses suggested that improvement of hypoalbuminemia occurs in most hypoalbuminemic patients who receive IDPN therapy and the likelihood and magnitude of the response to IDPN are associated with the severity of baseline hypoalbuminemia.

Dukkipati R, Kalantar-Zadeh K, Kopple JD. Is there a role for intradialytic parenteral nutrition? A review of the evidence. *Am J Kidney Dis.* 2010;55(2):352–364.

In this class review paper, the role of IDPN as an IV infusion of essential nutrients during hemodialysis treatment and its related studies are examined. Many studies have evaluated the effectiveness and safety of IDPN and show that IDPN has a good safety profile and also may improve protein-energy status. However, most studies have limitations in experimental design, such as small numbers of patients, lack of adequate controls, inclusion of patients without PEW, uncontrolled or unmonitored oral intake, nonrandomized design, or short duration. Thus, although IDPN may partially satisfy the nutritional needs of maintenance hemodialysis patients who have or are at risk of PEW, longer-term randomized prospective clinical trials with appropriate control groups are necessary to more definitively evaluate the clinical effectiveness and indications for IDPN.

Heidland A, Kult J. Long-term effects of essential amino acids supplementation in patients on regular dialysis treatment. *Clinical Nephrology.* 1975;3(6):234–239.

This classic paper highlighting a 1975 metabolic study of 18 patients in Germany receiving a high caloric diet with daily protein intake of 1 g/kg body weight demonstrated a decreased serum concentration of total protein, albumin, transferrin, and several components of the complement system. Long-term administration (60 weeks) of essential amino acids and histidine at the end of each hemodialysis improved the serum concentrations of the investigated proteins, whereas the serum concentration of inorganic phosphorus decreased slightly.

Hiroshige K, Iwamoto M, Kabashima N, Mutoh Y, Yuu K, Ohtani A. Prolonged use of intradialysis parenteral nutrition in elderly malnourished chronic haemodialysis patients. *Nephrol Dial Transplant.* 1998;13(8):2081–2087.

In this study, the effect of prolonged use of IDPN on malnutrition in 28 elderly hemodialysis patients was examined, and significant increases in serum albumin and transferrin concentrations and total lymphocyte count paralleled increases in protein-calorie intake beginning after

3 months of treatment and remained favorable throughout the study period. The investigators concluded that prolonged use of IDPN prevents muscle protein catabolism and promotes body protein and fat accumulation in malnourished elderly hemodialysis patients.

McCann L, Feldman MDC, Hornberger J, et al. Effect of intradialytic parenteral nutrition on delivered Kt/V. *Am J Kidney Dis.* 1999;33(6):1131–1135.

In 19 hemodialysis patients receiving IDPN who participated in this prospective, crossover study when patients received amino acid–containing solutions, mean Kt/V was significantly less than when IDPN was withheld. Administration of solutions without amino acids resulted in a mean Kt/V not significantly different from the mean Kt/V when IDPN was withheld.

Mortelmans AK, Duym P, Vandenbroucke J, et al. Intradialytic parenteral nutrition in malnourished hemodialysis patients: a prospective long-term study. *J Parenter Enteral Nutr.* 1999;23(2):90–95.

In 26 hemodialysis patients who, despite dietary advice and oral nutritional supplements, still had malnutrition, the feasibility and effects of a specific IDPN regimen were evaluated during a 9-month study period. Sixteen completed the study. IDPN resulted in a rise in body weight, which in part was attributable to an increase in body fat, without changes in plasma lipid levels.

Navarro JF, Mora C, León C, et al. Amino acid losses during hemodialysis with polyacrylonitrile membranes: effect of intradialytic amino acid supplementation on plasma amino acid concentrations and nutritional variables in nondiabetic patients. *Am J Clin Nutr.* 2000;71(3):765–773.

In 17 stable hemodialysis patients without diabetes, amino acid losses were evaluated over 2 weeks in 10 patients randomly assigned to receive amino acid supplementation. After administration of amino acids, the losses increased to 28 ± 4 g, while it produced a positive net balance of amino acids of 10.6 ± 5.6 g, preventing a reduction in plasma concentrations, and favorably affected the nutritional status of patients.

Piraino AJ, Firpo JJ, Powers DV. Prolonged hyperalimentation in catabolic chronic dialysis therapy patients. *J Parenter Enteral Nutr.* 1981;5(6):463–477.

Plasma concentrations of 25 essential and nonessential amino acids were measured predialysis and postdialysis in 46 hemodialysis patients, including 16 patients with prior weight loss of 14.5 ± 2.37 lb in 24 months, who were administered an amino acid solution for 20 weeks during each dialysis therapy. The study showed that this hyperalimentation improved some nutritional measures including plasma phosphoethanolamine level as a marker for catabolism.

Smolle KH, Kaufmann P, Holzer H, Druml W. Intradialytic parenteral nutrition in malnourished patients on chronic haemodialysis therapy. *Nephrol Dial Transplant.* 1995;10(8):1411–1416.

The effects of IDPN were evaluated in 16 malnourished hemodialysis patients. After a run-in period of 4 weeks, 0.8 g amino acids/kg bodyweight using a special amino acid solution adapted to metabolic alteration of uremia and including the dipeptide glycyl-tyrosine as tyrosine source was infused thrice weekly during each hemodialysis session for 16 weeks, which improved visceral protein status and stimulated immunocompetence in malnourished patients on regular hemodialysis therapy.

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Nutritional Management in Peritoneal Dialysis

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Protein-Energy Wasting

Patients with chronic kidney disease (CKD) are at risk for development of protein-energy malnutrition. The expert panels from the International Society of Renal Nutrition and Metabolism (ISRNM) first coined the term *protein-energy wasting* (PEW) to describe the malnutrition often seen among patients with CKD in 2007. PEW is specifically defined as the syndrome of depletion of systemic body protein and energy stores with specific diagnostic criteria. In this chapter, we will use PEW as an inclusive syndrome that also comprises protein and energy malnutrition and the complications associated with insufficient intake and increased catabolism seen in kidney disease patients.

Diagnosis and Assessment of Protein-Energy Wasting in Peritoneal Dialysis Patients

The ISRNM recommends using four separate criteria to diagnose PEW. These criteria include commonly utilized laboratory data, body mass measurement, muscle mass, and records of dietary intake to evaluate nutritional status. While not without some caveats, these criteria can be applied to peritoneal dialysis (PD) patients for the diagnosis of PEW and are summarized in Table 36.1.

Serum Chemistry

Serum albumin is the most essential diagnostic criterion for PEW in CKD. Among PD patients, albumin per se has been shown to be negatively and linearly associated with mortality and poor outcomes. Importantly, low serum albumin levels in PD patients are not specific for PEW. Albumin level often fluctuates with volume status, and hypoalbuminemia is caused by protein loss in dialysis effluent and may occur without obvious signs of infection or inflammation. Nevertheless, hypoalbuminemia remains a powerful indicator of PEW and a significant prognosticator of long-term outcome. Because of its limitations, the National Kidney Foundation Kidney-Disease Outcomes and Quality Initiative (NKF-KDOQI) nutrition guideline also recommend the use of additional markers to evaluate PEW. Other useful laboratory measures to evaluate malnutrition and inflammation often include C-reactive protein, leptin, adiponectin, and prealbumin (also known as transthyretin). However, many of these laboratory markers are also prone to fluctuations due to inflammation or infection. Hence, to properly assess nutritional status, one should always evaluate the presence of any active inflammation because it will likely lead to anorexia and PEW. While low cholesterol level may be another surrogate marker for low oral intake, one needs to be cognizant of the abnormal lipid metabolism in kidney disease as well as the ubiquitous use and effect of lipid-lowering agents.

Body Mass

The diagnostic criteria for PEW includes an absolute body mass index (BMI) $< 23\,kg/m^2$ or unintentional weight loss or low body fat. As in other CKD patients and those treated with hemodialysis (HD), the paradoxical relationship between high BMI and mortality, known as obesity paradox, is similarly observed among PD patients, albeit the findings are less consistent across studies. PD patients with low BMI have the highest risk for mortality, while higher BMI tends to be associated with a lower risk for death. It is important to know that in the general population, a BMI between 18.5 and $25\,kg/m^2$ may be considered the normal range, whereas ISRNM has suggested that a BMI $< 23\,kg/m^2$ is in the lower range for dialysis patients.

Muscle Mass

Muscle mass is an important criterion for the diagnosis of PEW. Surrogates for muscle mass may be extrapolated from anthropometric measurements of mid-arm muscle

TABLE 36.1 Clinical Criteria for Protein-Energy Wasting Diagnosis in Dialysis Patients

Serum Chemistry

Serum albumin < 3.8 g/dL

Transthyretin (prealbumin) < 30 mg/dL in dialysis patients

Serum cholesterol < 100 mg/dL

Body Mass

BMI (edema free) < 23 kg/m^2

Unintentional weight loss over time: 5% over 3 months or 10% over 6 months

Total body fat percentage < 10%

Muscle Mass

Muscle wasting: reduced muscle mass 5% over 3 months or 10% over 6 months

Reduced mid-arm muscle circumference by 10% in relation to 50th percentile of reference population)

Lower than expected serum creatinine

Dietary Intake

Unintentional low DPI < 0.80 g/kg/day for at least 2 months for dialysis patients or < 0.6 kg/day for patients with CKD stages G2–5

Unintentional low DEI < 25 kcal/kg/day for at least 2 months

At least three out of the four listed categories (and at least one test in each of the selected category) must be satisfied for the diagnosis of kidney disease-related PEW. Optimally, each criterion should be documented on at least three occasions, preferably 2–4 weeks apart.

a. Not valid if low concentrations are due to abnormally great urinary or gastrointestinal protein losses, liver disease, or cholesterol-lowering medicines.
b. A lower BMI might be desirable for certain Asian populations; weight must be edema-free mass, for example, postdialysis dry weight. See text for the discussion about the BMI of the healthy population.
c. Measurement must be performed by a trained anthropometrist.
d. Creatinine appearance is influenced by both muscle mass and meat intake.
e. Can be assessed by dietary diaries and interviews, or for protein intake by calculation of normalized protein equivalent of total nitrogen appearance (nPNA or nPCR) as determined by urea kinetic measurements.

BMI, Body mass index; *CKD*, chronic kidney disease; *DEI*, dietary energy intake; *DPI*, dietary protein intake; *nPCR*, normalized protein catabolic rate; *nPNA*, normalized protein of nitrogen appearance.
Adapted from Fouque D, Kalantar-Zadeh K, Kopple J, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int*. 2008;73(4):391-398.

circumference, waist circumference, or validated equations using serum creatinine. Serum creatinine is a useful surrogate of muscle mass in kidney failure patients when there is no residual kidney function. Studies have demonstrated that a very low creatinine level, < 4.0 mg/dL and 4.0–5.9 mg/dL, indicated a higher risk of death among PD patients with vintage > 1 year. Among PD patients, lean body mass has been found to correlate with creatinine kinetics, anthropometry, and bioelectrical impedance, but there are conflicting results on whether it may represent steady-state nutritional status or if it can prognosticate long-term outcomes.

Dietary Intake

PD patients with persistently low protein intake < 0.8 g/kg/day or daily energy intake < 25 kcal/kg/day are at particularly high risk for PEW. The estimation of caloric or protein intake is best estimated by a food intake diary or by normalized protein of nitrogen appearance (nPNA), also known as normalized protein catabolic rate (nPCR), as discussed later.

Other tools for PEW assessment recommended by the ISRNM are utilized commonly among clinicians and researchers during the care of PD patients. The following are examples of nutrition screening tools.

Normalized Protein of Nitrogen Appearance (Also Known as Normalized Protein Catabolic Rate)

Among patients in a steady state, urea nitrogen appearance is calculated to estimate daily protein intake, and nPNA can be used to estimate protein intake. In PD patients, protein of nitrogen appearance (PNA) can be calculated by estimating the generation of urea nitrogen in the dialysate and then normalized based on body weight. However, it is important to note the limitations of nPNA in PD. For example, among patients receiving intraperitoneal amino acid exchanges, the nPNA may be falsely elevated, giving an incorrect impression of a better nutritional state. Therefore, nPNA should be used in collaboration with other criteria to provide an accurate reflection of nutritional status.

Body Composition

Dual-energy x-ray absorptiometry or bioelectrical impedance analysis can be useful tools that inform clinicians of patients' volume status and anthropometry. However, they are not often readily available for clinical use in most dialysis clinics. Importantly, intra-abdominal dwells of dialysate solutions will also change the accuracy of the bioimpedance measurement, and patients need to have the peritoneal dialysate drained prior to this measurement. Thus, bioelectrical impedance is not currently recommended for body composition assessment in PD.

Nutritional Assessment Scores

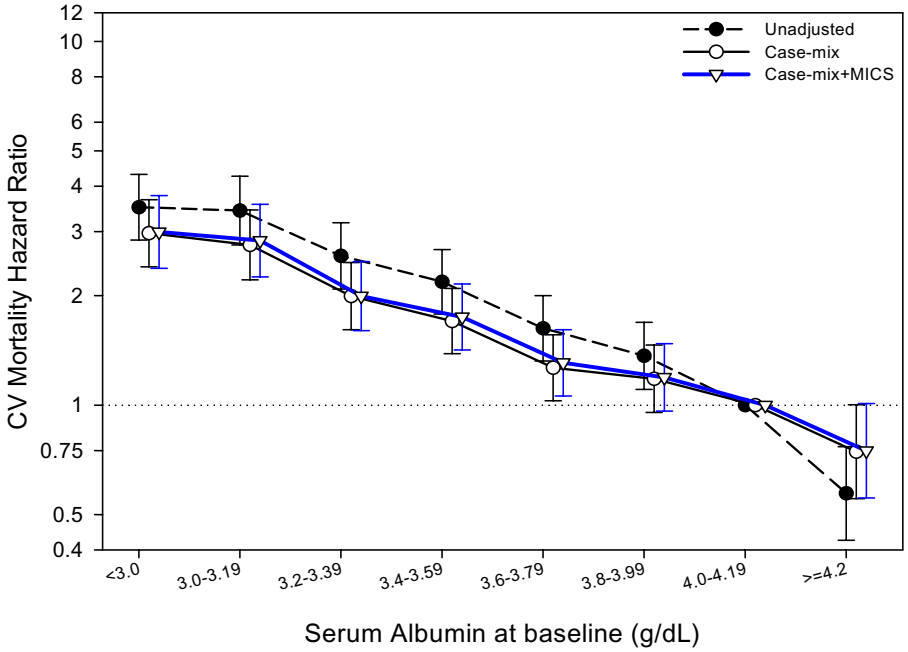
Subjective global assessment (SGA), a nutritional status assessment based on history and physical exam, has been validated in PD patients and found to be strongly associated with mortality. For every one-unit increase in the seven-point SGA, there was a 25% lower 2-year mortality risk ($p < 0.05$). The Malnutrition-Inflammation Score (MIS), also known as Kalantar Score, which incorporates components of the SGA, laboratory measurements including albumin and transferrin, and BMI, has also been found

to be well correlated with mortality and morbidity risk among HD patients. The use of MIS has also been significantly associated with other measures of PEW and is associated with long-term mortality in PD patients. Thus, it is a useful patient care tool and a prognosticating instrument for PD patients.

Epidemiology and Clinical Outcomes

Based on the previous diagnostic criteria, studies have evaluated the incidence and prevalence of PEW in CKD. By the time patients with CKD progress to kidney failure that requires dialysis initiation, the prevalence of PEW is particularly high. Almost half of patients treated with maintenance dialysis have mild to moderate PEW. A meta-analysis of 90 studies evaluating the global prevalence of PEW in kidney disease noted that 28%–54% of dialysis patients present with PEW. The prevalence of PEW is higher with greater severity of CKD. In this study, dialysis modality was not a statistically significant factor for the prevalence of PEW. On the contrary, a Korean study evaluated PD and HD patients using five different measures incorporating albumin, bodyweight loss, and symptoms. Approximately 82% of HD patients were considered well nourished, while 67% of PD patients did. However, long-term comparative analyses have shown that the trend does not necessarily persist as patients continue PD treatment in comparison with those treated with HD. Thus, decisions regarding modality selection should not be based on the patient's nutritional status alone.

Many studies have repeatedly shown that PEW is the strongest predictor of patient outcomes in kidney failure. Among patients treated with PD, the prognostic role of nutrition in patient outcomes has been demonstrated in clinical trials and observational studies. The ADEquacy of PD in MEXico (ADEMEX) study trial noted that patients with better nutritional status, represented by higher nPNA, had better survival. Lower albumin level was also associated with worse outcomes. The largest study of the association of serum albumin and mortality in PD patients was performed by Mehrotra et al. in 12,850 PD patients who were examined from 2001 and 2007 in the United States. Comparison with over 100,000 HD patients showed that in both PD and HD patients, serum albumin has by far the strongest association with mortality so that even a 0.1 to 0.2 g/dL higher or lower serum albumin or any such minor change in serum albumin over time in PD patients is associated with greater and worse survival, respectively (see Fig. 36.1). In the prospective cohort study of 14 clinical centers in the Canada–USA Peritoneal Dialysis (CANUSA) study, patients with lower serum albumin and lower SGA scores had a higher risk for mortality. In fact, with every unit decrease in the SGA score, the risk of 2-year mortality was higher by 25%. Over the last few years, multiple large cohort studies also demonstrated nutritional state markers, including low albumin, low prealbumin, low SGA, anorexia, and low nPCR, are independently and strongly associated with higher frequency of cardiovascular events, depression, poor quality of life, and worse long-term survival.



• **Fig. 36.1** Association of Baseline Serum Albumin Concentration With Cardiovascular Outcomes in Patients Undergoing Peritoneal Dialysis (n = 12,171). Reference group: peritoneal dialysis patients with serum albumin between 4.00 and 4.19 g/dL. *CV*, Cardiovascular; MICS, malnutrition-inflammation complex syndrome. (Adapted from Mehrotra R, Duong U, Jiwakanon S, et al. Serum albumin as a predictor of mortality in peritoneal dialysis: comparisons with hemodialysis. *Am J Kidney Dis*. 2011;58(3):418–428.)

Importantly, the association of poor nutritional state and clinical outcome may not be a cause-and-effect relationship in these studies. Malnutrition and low albumin may be a result or are surrogate markers of other complications of dialysis or intercurrent illnesses. Nevertheless, PEW per se may be contributing to the overall poor outcomes. Independent of the cause of PEW, nutritional support is important to improve PEW and outcomes.

Given that PEW is associated with higher mortality and morbidity in the PD population, it is important to understand what CKD-specific factors contribute to PEW. PD modality also presents modifiable risk factors that may be corrected to prevent and treat PEW.

Risk Factors for Protein-Energy Wasting in Peritoneal Dialysis Patients

The causes and manifestations of PEW in CKD are well described. Fig. 36.2 shows the relationship between KDIGO staging of CKD and contribution of relative factors to PEW. Complications associated with uremic, such as poor nutritional intake, anorexia, volume overload, oxidative and carbonyl stress, as well as other comorbidities including diabetes, infection, and endocrine disorders can all contribute to PEW. Fig. 36.3 demonstrates a more precise etiological map of the causal factors of PEW in CKD and kidney failure patients. Other causes implicated in the development of PEW syndrome in geriatric dialysis patients include limited income, social isolation, lack of understanding of nutritional requirement, malabsorption and gastrointestinal (GI) motility disorders, ill-fitting dentures, depression, lower cognition, limited access to food, impaired taste, smell, anorexia, constipation, and frequent hospitalizations.

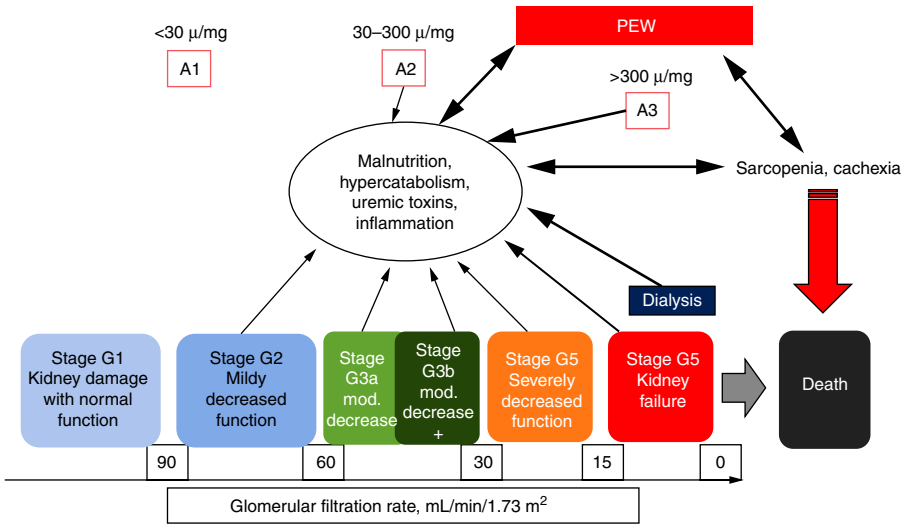
Additionally, PD patients face unique challenges that contribute to PEW, and a summary is provided in Table 36.2. Here, we discuss a few specific contributors to PEW in PD.

Protein Loss

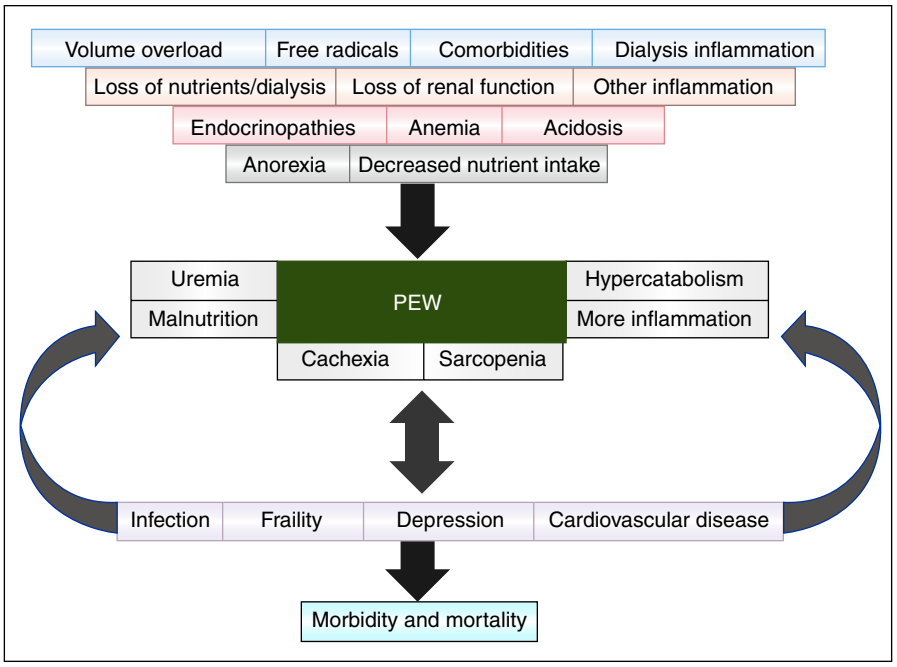
Turnover of albumin is often increased in dialysis patients due to increased external losses, while there are compensatory increases in hepatic albumin synthesis. The normal rate of increase of albumin synthesis is about 12 g/day. Approximately 5–6 g of protein is lost through the peritoneal membrane daily, and this loss is higher with longer dwell time and number of exchanges in automated peritoneal dialysis (APD). Patients with high peritoneal-membrane solute-transfer rates are also particularly at risk with more albumin loss, resulting in lower serum albumin levels.

Glucose Absorption

Absorption of carbohydrates from dextrose-based dialysate can contribute to a significant proportion of total daily energy intake, often up to 500–800 kcal/day depending on the type of dextrose concentration, peritoneal solute transfer rate, and dwell time. Up to 60% of daily dialysate glucose load may be absorbed, resulting in glucose absorption of 100 to 200 g/day. This significant amount of caloric intake may contribute to lower appetite and, subsequently, poor oral intake. Increased glucose absorption also leads to hyperinsulinemia, insulin resistance, dyslipidemia, oxidative stress and inflammation, increased hyperglycemia, and insulin requirement in PD patients with diabetes mellitus (DM).



• **Fig. 36.2** Conceptual Model of Protein-Energy Wasting and Relative Contribution of CKD to Various Physiological Factors as Renal Disease Progresses. *A*, Proteinuria KDIGO stage; *CKD*, chronic kidney disease; *G*, KDIGO glomerular filtration stage; *KDIGO*, Kidney disease improving global outcome; *mod.*, moderate (G3b is associated with more advanced CKD than G3a; hence, it is labeled as moderate +). (Adapted from Hanna R, Ghobry L, Wassef O, Rhee CM, Kalantar-Zadeh K. A practical approach to nutrition, protein-energy wasting, sarcopenia, and cachexia in patients with chronic kidney disease. *Blood Purif.* 2020;49:202–221.)



• **Fig. 36.3** Interaction of Pathological Factors That Produce a Protein-Energy Wasting State in CKD. CKD-related factors that reinforce the deterioration of nutritional status and overall health. *CKD*, chronic kidney disease; *PEW*, protein-energy wasting. (Adapted from Hanna R, Ghobry L, Wassef O, Rhee CM, Kalantar-Zadeh K. A practical approach to nutrition, protein-energy wasting, sarcopenia, and cachexia in patients with chronic kidney disease. *Blood Purif*. 2020;49:202–211.)

Inflammatory States

Chronic inflammation is common in dialysis patients and leads to PEW with increased protein catabolism. Among PD patients, inflammation may be exacerbated due to the underlying cause of kidney disease, episodic infections, peritonitis or increased exposure to glucose, and subsequent generation of advanced glycation products, which may be associated with inflammatory cytokines and appetite suppression. Glucose degradation products may also induce the formation of advanced glycation end products (AGEs), which can lead to fibrosis and microvascular sclerosis.

Another cause of inflammatory state in PD patients is peritonitis. Peritonitis is a major, although now infrequent, complication of PD that contributes to technique failure and mortality in PD patients. During episodes of peritonitis, the inflammatory changes to the membrane may result in up to 20 g of albumin losses in the effluent. This will directly lead to lower serum albumin levels, especially if patients do not increase protein intake. The inflammation and decreased oral intake associated with an infectious episode may directly contribute to PEW. Importantly, while peritonitis can lead to PEW, PEW is also a major risk factor for the development of peritonitis. In a meta-analysis of 35 studies, it was found that patients with hypoalbuminemia had significantly higher risk of developing peritonitis.

Gastrointestinal Complications of Peritoneal Dialysis

Intra-abdominal fluid can lead to abdominal discomfort, a sensation of fullness, and possibly delayed gastric emptying, which may further exacerbate PEW in PD patients. PD patients report symptoms of indigestion, gastric reflux, and discomfort. This can lead to lower peak hunger, less change in fullness rating, and lower nutrient intakes. Additionally, encapsulating peritoneal sclerosis (EPS) is a rare complication of PD. It is an important etiology of acute and chronic inflammation that can lead to PEW. More significantly, EPS patients often have associated bowel obstructions or strangulation, resulting in decreased oral intake and poor absorption of nutrients. The treatment options include episodic bowel rest or surgeries, which may further exacerbate the decreased oral intake and malnutrition.

Management of Protein-Energy Wasting in Peritoneal Dialysis Patients

Daily Energy Intake Goal

The 2000 KDOQI guideline recommends a total daily energy intake of 35 kcal/kg/day for patients 60 years of age or younger and 30–35 kcal/kg/day for those who are older, while the upcoming updated 2020 KDOQI guideline recommends 25–35 kcal/kg per day. As discussed earlier, the high amount of absorbed glucose may reduce patient appetite, which may be partially ameliorated by the dialysate glucose absorption. Importantly, there are no interventional trials evaluating the recommended calorie intake and correlating this with outcomes among PD patients. Thus, it is key to take into account factors that may affect patients' energy needs and customizes patient prescription

TABLE 36.2 Causes of Protein-Energy Wasting in Peritoneal Dialysis Patients

Inadequate Nutrient Intake

Anorexia Caused by

Uremic toxicity

Impaired gastric emptying

Inflammation with/without comorbid conditions*

Emotional and/or psychological disorders

Dietary Restrictions

Prescribed restrictions: low-potassium low-phosphate regimens

Social constraints: poverty, inadequate dietary support

Physical incapacity: inability to acquire or prepare food or to eat

Nutrient Losses during Dialysis

Loss into peritoneal dialysate

Hypercatabolism Caused by Comorbid Illnesses

Cardiovascular diseases*

Diabetic complications

Infection and/or sepsis*

Other comorbid conditions*

Hypercatabolism Associated With Dialysis Treatment

Negative protein balance

Negative energy balance

Endocrine Disorders of Uremia

Resistance to insulin

Resistance to growth hormone and/or IGF-1

Increased serum level of or sensitivity to glucagons

Hyperparathyroidism

Other endocrine disorders

Adapted from Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD. Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. *Am J Kidney Dis*. 2003;42(5):864-881.

of daily energy intake goal. Fig. 36.4 depicts our suggested algorithm for the management of nutritional status in PD patients.

Daily Protein Intake

The 2020 KDOQI guideline has recommended a daily protein intake of 1.2 to 1.3 g/kg/day for stable PD patients, while the updated 2020 KDOQI guideline recommends 1.0–1.2 g/kg/day for stable PD patients. This recommendation remains a matter of debate, especially because it may lead to a higher dietary phosphate load, a higher risk of metabolic acidosis, faster decline of residual kidney function, and a higher probability of increased fluid intake. Nevertheless, recent data examining the impact of dietary phosphate counseling efforts on dialysis patients noted that restriction of dietary phosphate intake could lead to lower dietary protein intake and worse nutritional status. Interestingly, a large long-term Chinese study has reported higher plant-based protein with lower cardiovascular outcomes and mortality. Further interventional studies in the use of plant-based protein in PD will be needed to confirm this finding.

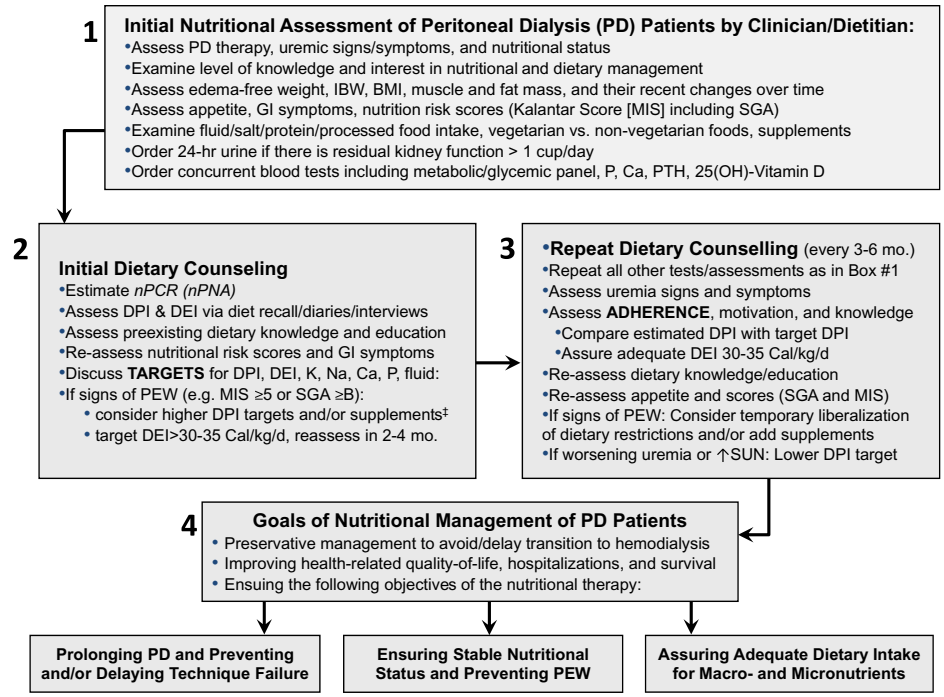
Dialysis Prescription and Metabolic Acidosis

While most randomized controlled trials have not shown a direct benefit of high PD dosage on nutritional status or outcomes, the ADEMEX study did find that those who achieved a higher Kt/V target had a higher nPNA level. Notably, Kt/V and nPNA are mathematically linked, and the improvement of nPNA may not implicitly represent better nutritional status. Thus, it remains unclear whether a change in PD prescription to improve adequacy would result in less PEW. Importantly, patients who usually have maintained residual kidney function have better nutritional status. Therefore, an effort to maintain residual kidney function is paramount. The assessment of dialysis adequacy and residual kidney function should be performed regularly.

While mild metabolic acidosis may be observed among patients with excellent protein intake, more severe degrees of metabolic acidosis with serum bicarbonate level less than 19 mmol/L is likely a complication of kidney failure and possibly inadequate dialysis. As acidosis may further worsen protein catabolism, it is a potentially reversible and treatable factor. A change in the prescribed dialysate buffer level may be beneficial. Correction of acidosis with a more alkaline PD fluid or treatment with oral sodium bicarbonate has been evaluated in randomized controlled studies and has been shown to result in improved bicarbonate levels, preserved residual kidney function, nutritional status, and fewer hospitalizations. Thus, oral sodium bicarbonate supplementation may serve as an important therapeutic tool to improve nutritional status.

Intraperitoneal Nutrition

Intraperitoneal amino acid supplementation is an option for PD patients with severe PEW. Intraperitoneal nutrition (IPN) can be provided in different combinations; a more commonly used mixture includes 15 amino acids (9 essential and 6 nonessential amino acids) that are added to a peritoneal dialysate solution, resulting in a 1.1% amino acid solution with reduced glucose concentration. This may reduce net amino acid loss and the infused carbohydrate



• **Fig. 36.4** Suggested Algorithm for the Management of Nutritional Status in Peritoneal Dialysis Patients. *BMI*, body mass index; *DEI*, dietary energy intake; *DPI*, dietary protein intake; *GI*, gastrointestinal; *IBW*, ideal body weight; *MIS*, Malnutrition-Inflammation Score; *nPCR*, normalized protein catabolic rate; *nPNA*, normalized protein of nitrogen appearance; *PD*, peritoneal dialysis; *PTH*, parathyroid hormone; *SGA*, subjective global assessment; *SUN*, serum urea nitrogen.

load. There is limited impact of using one or two exchanges with 1.1% amino acid dialysate to treat PEW in PD. Small studies have shown some benefit in total protein and energy intake, although data on long-term nutritional status and clinical outcome are not available. It is also unclear if patients in significant inflammatory and catabolic states will be able to incorporate the additional amino acids into protein synthesis. While intra peritoneal amino acid dialysate may be a potentially useful method to treat PEW in PD patients, the clinician must remain cognizant of potential side effects, including metabolic acidosis, worsening uremia, and further reduction of oral intake.

Appetite and Hormonal Stimulants

The use of appetite stimulants including megestrol acetate, cannabinoids, pentoxyphylline, and certain appetite-stimulating antidepressants such as mirtazapine has not been systematically evaluated in large interventional trials in PD. However, in small studies, 160 mg of oral megesterol daily increased weight gain and serum albumin after 3 months. Nonetheless, megestrol is associated with serious adverse events, including hypogonadoism, adrenal insufficiency, and increased thrombosis risk. Other agents such as recombinant human growth hormone (rhGH) and insulin-like growth factor-I have been studied in a small number of PD patients. The short-term studies suggested potential anabolic effects. However, no long-term studies are available to evaluate further the effect to prevent or treat PEW. Thus, short-term use of appetite stimulants may be considered as a treatment option.

Dietary Counseling

The 2000 and 2020 NKF-KDOQI guideline recommended a registered dietitian to monitor and evaluate CKD 3–5D and posttransplant patients' nutritional status. Every PD patient should receive nutritional education and interventions by a dietitian, who can provide assessment and monitoring of the PD patient's appetite, dietary behavior, weight change, biochemical data, and nutrition-focused physical exam. Some PD patients may have difficulty achieving recommended goals, especially if they are transitioning from a recommended low-protein diet prior to dialysis initiation. An individualized diet plan for a PD patient should take into consideration the PD prescription, membrane characteristics, evaluation of glucose absorption, and protein loss in the effluent, not to mention the social, cultural, and dietary preferences of the PD patient. As physicians and dietitians may impose dietary restrictions on their patients regarding dietary phosphate, sodium, and fluid intake, patients may find it quite challenging to find suitable food choices, thus worsening PEW. Hence, nutritional education and patient empowerment on the choice of food with higher protein-to-phosphate ratio, required carbohydrate intake, and weight management are also paramount.

Oral and Enteral Nutritional Supplementation

The effectiveness of oral nutritional supplements has not been well established in large randomized controlled trials among PD patients. Many small studies have demonstrated that oral supplementation increases the protein and caloric intake of PD patients, as well as improves albumin and anthropometric parameters. However, the long-term effect on PD patient outcomes has not been studied. Thus, the updated NKF-KDOQI guideline recommends a minimum of a 3-month trial of oral nutritional supplement if dietary counseling alone is inadequate.

The use of tube feeding, including intermittent nasogastric tube or percutaneous endoscopic gastrostomy (PEG) tube feeding in PD, is rarely recommended. In a few case series where adult and pediatric patients received PEG tube feedings for supplemental nutrition, the risk of complications was high, including the development of bleeding and fatal and nonfatal peritonitis. Thus, PEG tube feeding should be considered as a last resort in PD patients with severe PEW.

Conclusion

PEW is a common phenomenon in kidney failure patients receiving PD treatment and is associated with poor long-term prognosis. Development of PEW may be associated with kidney disease itself, chronic or acute inflammatory states, and modality-associated factors. A comprehensive nutritional assessment should include the use of laboratory measures, dietary records, and validated instruments. Clinicians need to be aware of the caveats of these tools when they are used to diagnose and monitor treatment of PEW. Frequent assessment of nutritional status is important. Treatment options should include intensive and individualized dietary counseling with specific dietary protein and energy intake goals. Dialysis adequacy and metabolic acidosis may be corrected, as these conditions will likely exacerbate PEW. More interventional trials that include multimodal therapy to include nutritional support, intraperitoneal amino acid, or additional anabolic agents are needed to evaluate long-term effects in PD patients with severe PEW.

Recommended Reading

Chan JY, et al. Comprehensive malnutrition inflammation score as a marker of nutritional status in Chinese peritoneal dialysis patients. *Nephrology (Carlton).* 2007;12(2):130–134.

In this study, 165 adult PD patients underwent assessment by MIS (or Kalantar Score) and the 7-point SGA score. Patients with limited self-care capability, diabetes, and multiple comorbidities had worse score (i.e., worse nutrition) revealed by SGA than by MIS, while patients who had been dialyzed longer had worse score revealed by MIS than by SGA.

Cheng TH, et al. Serial monitoring of nutritional status in Chinese peritoneal dialysis patients by subjective global assessment and comprehensive Malnutrition Inflammation Score. *Nephrology (Carlton).* 2009;14(2):143–147.

The change in Kalantar Score (MIS) and SGA was examined in 59 PD patients. The longitudinal changes in the MIS and SGA scores have modest agreement with each other, while PD patients with a longer duration of dialysis, higher serum ferritin, total iron-binding capacity (TIBC), total Kt/V, or normalized protein nitrogen appearance tended to have discrepancies between the longitudinal changes in the MIS and SGA overall score.

de Mutsert R, et al. Association between serum albumin and mortality in dialysis patients is partly explained by inflammation, and not by malnutrition. *J Ren Nutr.* 2009;19(2):127–135.

In this prospective cohort study of incident dialysis patients starting HD or PD in the Netherlands, a 1-g/dL decrease in serum albumin was associated with an increased mortality risk of 47% in HD patients and 38% in PD patients.

Hanna RM, Ghobry L, Wassef O, Rhee CM, Kalantar-Zadeh K. A practical approach to nutrition, protein-energy wasting, sarcopenia, and cachexia in patients with chronic kidney disease. *Blood Purif.* 2020;49(1-2):202–211.

This is a scholarly review of the PEW and management of nutrition and diet in the entire range of CKD including ESRD patients who are dialysis dependent.

Harty J, et al. Limitations of kinetic models as predictors of nutritional and dialysis adequacy in continuous ambulatory peritoneal dialysis patients. *Am J Nephrol.* 1993;13(6):454–463.

This study examined 147 stable PD patients and found that severely malnourished patients had significantly greater normalized clearance and adequacy values than well-nourished patients, which may explain the failure of such adequacy values to reflect outcome and argues against accepting such values as measures of dialysis well-being.

He T, et al. Malnutrition-Inflammation Score predicts long-term mortality in Chinese PD patients. *Clin Nephrol.* 2013;79(6):477–483.

The MIS or Kalantar Score, along with the SGA, was used to assess 155 stable PD patients and it was found that a one-unit increase in Kalantar Score was associated with a 1.27-fold greater death risk.

Ho LC, et al. Malnutrition-Inflammation Score independently determined cardiovascular and infection risk in peritoneal dialysis patients. *Blood Purif.* 2010;29(3):308–316.

In 141 PD patients, the MIS and Charlson Comorbidity Index (CCI) were both independent predictors of cardiovascular and infection events. The CCI, which is closely associated with the MIS, is an independent determinant of cardiovascular and infection events.

Kalantar-Zadeh K, et al. Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. *American Journal of Kidney Diseases.* 2003;42(5):864–881.

This is the inception study of the creation and validation of the MIS or Kalantar Score, in that MIS was found to be as strong predictor of survival.

Kalantar-Zadeh K, et al. Inflammation and nutrition in renal insufficiency. *Adv Ren Replace Ther.* 2003;10(3):155–169.

This is a classic review paper about the concepts of malnutrition-inflammation complex syndrome (MICS) and/or malnutrition-inflammation-atherosclerosis (MIA) in dialysis-dependent patients.

Kaysen GA. Serum albumin concentration in dialysis patients: why does it remain resistant to therapy? *Kidney Int.* 2003;Suppl(87):S92–S98.

This paper reviews the pathophysiologic mechanisms as to why a low serum albumin is difficult to correct in ESRD patients.

Mehrotra R, Duong U, Jiwakanon S, et al. Serum albumin as a predictor of mortality in peritoneal dialysis: comparisons with hemodialysis. *Am J Kidney Dis.* 2011;58(3):418–428.

This is the large study of the association of baseline serum albumin concentration with cardiovascular outcomes in 12,171 patients undergoing peritoneal dialysis.

Mehrotra R, Kopple JD. Protein and energy nutrition among adult patients treated with chronic peritoneal dialysis. *Adv Ren Replace Ther.* 2003;10(3):194–212.

In this review paper, the traditional concept of protein-energy malnutrition (PEM) in adult patients treated with chronic PD (CPD) is discussed.

Moretti HD, et al. Effects of protein supplementation in chronic hemodialysis and peritoneal dialysis patients. *J Ren Nutr.* 2009;19(4):298–303.

In 49 HD and PD patients, nPCR significantly increased by month 4 of treatment from a baseline of 1.05 to 1.16, and in-center supplementation of protein improved serum markers of nutrition in these patients.

Noori N, et al. Racial and ethnic differences in mortality of hemodialysis patients: role of dietary and nutritional status and inflammation. *Am J Nephrol.* 2011;33(2):157–167.

In this 6-year cohort study of 799 HD patients, significant racial disparities existed in dietary, nutritional, and inflammatory measures, which may contribute to HD outcome disparities.

Obi Y, et al. Latest consensus and update on protein-energy wasting in chronic kidney disease. *Curr Opin Clin Nutr Metab Care.* 2015;18(3):254–262.

In this review paper, the MIS (Kalantar Score) is reviewed along with other assessment tools for nutritional assessment of CKD patients. Prevention and treatment of PEW should involve individualized and integrated approaches to modulate identified risk factors and contributing comorbidities.

Park YK, et al. A cross-sectional study comparing the nutritional status of peritoneal dialysis and hemodialysis patients in Korea. *J Ren Nutr.* 1999;9(3):149–156.

This study was performed to compare the nutritional status of PD and HD patients in Korea and to validate the nutritional assessment method. It found that a higher incidence of malnutrition was observed in PD patients than in HD patients.

Shinaberger CS, et al. Is controlling phosphorus by decreasing dietary protein intake beneficial or harmful in persons with chronic kidney disease? *Am J Clin Nutr.* 2008;88(6):1511–1518.

This study suggested that the risk of controlling serum phosphorus by restricting dietary protein intake may outweigh the benefit of controlled phosphorus and may lead to greater mortality.

Stein A, et al. Role of an improvement in acid-base status and nutrition in CAPD patients. *Kidney International.* 1997;52(4):1089–1095.

This study found that better correction of metabolic acidosis leads to greater increases in body weight and mid-arm circumference, but not triceps skinfold thickness, in the first year of PD.

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Anemia and Its Treatment in Patients With End-Stage Kidney Disease

HITESH H. SHAH, MD • STEVEN FISHBANE, MD

Introduction

Anemia is an important clinical complication of chronic kidney disease (CKD). It is defined by the World Health Organization as serum hemoglobin level < 13 g/dL in adult men and postmenopausal women and < 12 g/dL in premenopausal women. Similar to anemia of chronic disease, anemia of CKD is generally normocytic and normochromic with bone marrow of normal cellularity. While several factors may play a contributing role in the development of anemia in CKD, relatively decreased secretion of erythropoietin from the diseased kidneys is a hallmark of the pathogenesis. As kidney function declines, there is a relative decrease in the production of erythropoietin leading to an increased prevalence of anemia. Data from the National Health and Nutrition Examination Survey (NHANES) conducted in 2007–2008 and 2009–2010 showed the prevalence of anemia to be increased with the stage of CKD, from 8.4% at stage 1 (glomerular filtration rate [GFR] ≥ 90 mL/min/1.73 m^2 plus evidence of kidney disease) to 53.4% at stage 5 (GFR < 15 mL/min/1.73 m^2). For patients requiring dialysis, the vast majority require erythropoiesis-stimulating agent (ESA) treatment for anemia.

Several clinically relevant consequences result from the development of anemia in patients with CKD. Many of the symptoms that were formerly attributed to advanced kidney failure and uremia were, in fact, at least in part due to anemia. The most notable symptoms include fatigue, reduced exercise tolerance, and dyspnea. Other common complaints with severe anemia include insomnia, loss of appetite, cold intolerance, and reduced sexual and cognitive function. Anemia is associated with and may lead to increased cardiac work and worsening of left ventricular hypertrophy, angina, and congestive heart failure. Other problems as a result of anemia include impaired immune and hemostatic function. It is not surprising, therefore, that anemia has also been associated with high morbidity and mortality in this population.

Treatment of anemia with ESAs in patients with non-dialysis CKD and end-stage kidney disease (ESKD) may not only decrease blood transfusion requirements but improve symptoms and may also help to enhance quality of life.

In this chapter, we will review causes of anemia and its treatment in patients with ESKD.

Causes of Anemia

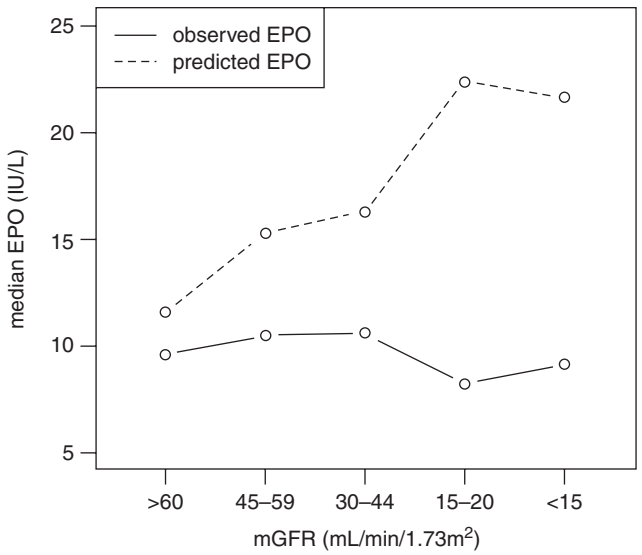
Erythropoietin Deficiency

The erythropoietic system functions to ensure an adequate supply of erythrocytes and hemoglobin to support the delivery of oxygen to the body's organs and tissues. When anemia or hypoxia develops, cells recognize oxygen deprivation, and a large group of genes is activated that protect cells from damage due to hypoxia. The process is mediated by stabilization of hypoxia-inducible factors (HIF). In the kidneys, activation of the HIF system plays a particularly important role by regulating the activity of renal erythropoietin-producing (REP) cells.

As the kidneys fail, erythropoietin deficiency develops. The deficiency is relative in that serum levels of erythropoietin are actually higher in CKD than among normal controls but lower than what the levels should be for the degree of anemia (Fig. 37.1). In ESKD, levels become frankly deficient, and most patients will require ESA therapy on a chronic basis.

Iron Deficiency and Inflammation

Most hemodialysis patients become iron deficient, which contributes to the development of anemia. Iron deficiency in these patients is multifactorial in origin. The most apparent cause is that blood (and iron) is lost during every hemodialysis treatment. There is blood retained in the dialysis filter and lines and occasional bleeding that occurs during and after the treatment. This has been estimated to result in 3–10 mg of iron lost per treatment. In addition, frequent blood draws for laboratory testing and blood loss during surgical or interventional procedures adds



• **Fig. 37.1** Mercadal et al. studied the serum erythropoietin *(EPO)* and hemoglobin at different levels of glomerular filtration rate. As CKD progressed, the observed EPO response lagged behind the expected response, indicating a state of relative deficiency of EPO. *CKD*, Chronic kidney disease; *mGFR*, measured glomerular filtration rate. (From Mercadal L, Metzger M, Casadevall N, et al. Timing and determinants of erythropoietin deficiency in chronic kidney disease. *Clin J Am Soc Nephrol*. 2012;7(1):35-42.)

to negative iron balance. Another source of blood loss is gastrointestinal bleeding, which is more common among dialysis patients and results in episodic worsening of iron deficiency.

In the early years of the ESA era, from 1989–1995, absolute iron deficiency (deficient bone marrow iron stores) was common. For example, in 1993, 54% of U.S. hemodialysis patients had transferrin saturation (TSAT) < 20% and 56% had serum ferritin < 200 ng/mL; 96% of patients had serum ferritin < 800 ng/mL. In contrast, in 2020, as a result of widespread intravenous (IV) iron treatment, 750 ng/mL is approximately the mean U.S. serum ferritin in hemodialysis patients. This indicates that absolute iron deficiency is probably much less common than it had been previously. But, there is still evidence of reduced iron availability, even when adequate iron storage is present. For example, treatment with IV iron may result in increased hemoglobin and reduced ESA dose requirements despite serum ferritin > 500 ng/mL. Clinically apparent iron deficiency in the presence of adequate iron storage is often termed *functional iron deficiency*.

One reason for functional iron deficiency is that during ESA treatment, even normal iron stores may not supply adequate iron for pharmacologically accelerated erythropoiesis. For example, most humans may have 2000–3000 mg of iron in their bodies. However, only approximately 1/1000 of this, about 2–3 mg, circulates in the bloodstream. During ESA treatment, this may not be enough iron to allow for production of iron-replete erythrocytes.

A second reason for functional iron deficiency relates to the liver-derived protein hepcidin, which serves as the body's primary regulator of iron homeostasis. During iron overload, hepcidin blocks intestinal iron absorption and release of iron from the body's storage tissues. In iron-deficient states, hepcidin production is reduced, and iron absorption and release from storage tissues are enhanced. In this way, hepcidin acts to maintain iron homeostasis.

Hepcidin has a secondary function beyond its iron homeostasis function. That is, its production is also increased potently in states of inflammation, independent of iron status. Although the stimulus for hepcidin production is different, the effect is the same, reduced iron availability. In patients with infections causing inflammation, this is an adaptive response that may limit iron available to microorganisms. In dialysis patients, inflammation is often present even without infection. The etiology is unclear, perhaps due to atherosclerosis, infection, uremic toxins, or other factors yet to be identified. As a result of the inflammation, many dialysis patients have reduced iron availability due to hepcidin induction. This form of functional iron deficiency may be maladaptive in that it makes anemia more difficult to treat with no clear positive effect on the patient. Because iron is blocked in storage tissues, serum ferritin may appear normal or high, while measures of circulating iron like TSAT may be normal to low.

Reduced Erythrocyte Survival

Red cell half-life is reduced among patients with advanced kidney disease. The exact magnitude of reduction has been difficult to characterize. While the normal red cell life is approximately 120 days, estimates in dialysis patients have been as low as 40–80 days. The mechanisms behind the reduced erythrocyte lifespan in ESKD patients have not been fully elucidated. Uremic toxins, low-grade hemolysis due to shearing by dialysis needles, and other factors have all been implicated. Shortened erythrocyte half-life (for example, due to hemolysis) can be compensated for in nonuremic individuals through accelerated erythrocyte production. In patients on dialysis, erythropoietin deficiency limits this ability.

Infection

Infection contributes to anemia in ESKD patients. Increases in serum hepcidin and reduced availability of iron for erythropoiesis (as described above) play important roles. In addition, infection by itself may interfere with red cell production. Certain infections can also cause hemolysis, leading to red cell loss. Hemoglobin concentrations often decrease in chronic infections but may decline in acute infections as well. One interesting source of occult infection seen in dialysis patients occurs in previously used but currently nonfunctioning arteriovenous grafts. These infections are hard to detect but may be an important cause of ESA hyporesponsiveness.

Hyperparathyroidism

Hyperparathyroidism contributes to the anemia of CKD, at least in part due to fibrosis of the bone marrow. The best proof of this relationship may be that after parathyroidectomy, anemia tends to improve whether hyperparathyroidism was primary or secondary to other factors. The decision on whether parathyroidectomy is necessary should not be based on anemia but rather on more traditional mineral and bone parameters. Medical treatment of hyperparathyroidism does appear to have a beneficial effect on anemia. Goicoechea et al. treated 28 patients with hyperparathyroidism with IV-activated vitamin D therapy. The result of treatment was an improvement in hemoglobin concentration and reduction in ESA dose requirements.

Bleeding

Acute or chronic blood loss from either an occult or obvious clinical source may contribute to anemia of CKD. This is a particularly important cause in that treatment of the underlying cause may be necessary. The usual response to worsening anemia in dialysis patients is to increase the ESA dose, often without a clinical evaluation. As a result, the diagnosis of occult blood loss may be significantly delayed. Accordingly, whenever there is worsening of anemia or ESA hyporesponsiveness, there should be an evaluation for the possibility of blood loss, including, as appropriate, testing for gastrointestinal bleeding.

Other Hematologic Disorders

Because of the primacy of erythropoietin deficiency as a cause of anemia in ESKD and because of mechanical ESA dose adjustment protocols, the response to worsening anemia is usually repetitive increases in ESA dose. As discussed earlier, this may delay evaluation for occult bleeding. However, evaluation for other causes of anemia may also be delayed. Patients with ESKD may develop any of a large number of causes of anemia that individuals in the general population are subject to.

When a dialysis patient has reduced responsiveness to an ESA, then a basic anemia evaluation is called for. After ruling out iron deficiency and other issues discussed earlier, pathologic causes of reduced red cell production, sequestration, and hemolysis should be considered. Erythrocyte production defects can result from folic acid or vitamin B_{12} deficiency, among many other causes. Myelodysplasia is an important cause of anemia in older individuals and should be considered in ESKD patients resistant to ESA treatment.

An epidemic of pure red cell aplasia due to antierythropoietin antibodies took place primarily in Europe in the late 1990s. Rare sporadic cases may still occur. Hemolytic conditions can be acute during hemodialysis, but chronic hemolytic conditions should be considered when unexplained anemia is present and suggestive clinical signs are present. In general, when a response to ESA therapy is suboptimal and typical causes have been excluded, further evaluation with red cell indices, reticulocyte count, folic acid, vitamin B_{12} level, C-reactive protein, lactate dehydrogenase, and bilirubin should be completed. If the cause of ESA hyporesponse remains undetermined, hematologic consultation should be considered.

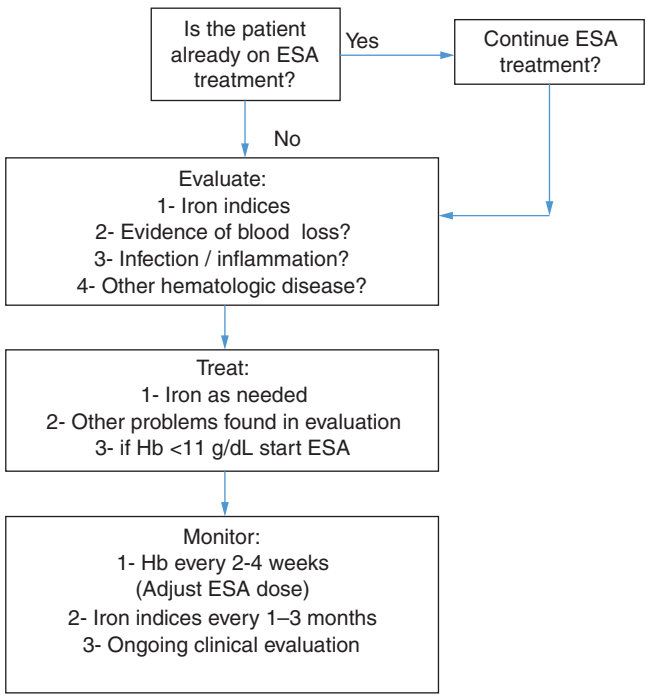
Evaluation and Treatment of Anemia in Patients on Dialysis

Introduction to Treatment

The treatment of anemia in ESKD includes ongoing monitoring of hemoglobin, ESA dose, and iron status. Unless the hemoglobin is very low at the initiation of dialysis, in which case blood transfusion might be required, there is no immediate need to initiate anemia treatments. If the patient is already receiving ESA and/or iron therapy, it could be continued. If not, then the patient's anemia should be evaluated as discussed earlier before starting treatment. This allows for the best opportunity for assessing the causes of the patient's anemia and helping select treatments (Fig. 37.2). Before discussing specific treatments, we will first review the goals of therapy.

Goals of Anemia Management

Prior to the availability of ESAs, patients on dialysis had moderate to severe anemia that often resulted in dependence on blood transfusions. It is remarkable to note that



• **Fig. 37.2** Anemia Management at the Initiation of Dialysis. *ESA*, Erythropoiesis stimulating agent.

in Eschbach's seminal 1989 phase 3 study that led to the approval of epoetin alfa, the 333 patients had received 1030 blood transfusions in the 6 months prior to treatment. After epoetin treatment, the transfusion rate decreased to virtually none. This should serve as a reminder that anemia in ESKD, when untreated, is often severe and that ESA treatment was revolutionary in the ability to raise hemoglobin concentrations and reduce the need for blood transfusions.

Since anemia can cause uncomfortable symptoms, including fatigue and shortness of breath, patients should be questioned on their sense of well-being. The accumulated symptoms can degrade overall quality of life. Patients may restrict activities to compensate for diminished capabilities. Because the symptoms are nonspecific, it can be very difficult to determine the degree to which anemia is the specific cause. The patient's overall medical condition should be considered in the context of the anemia evaluation. To the extent that anemia is believed to contribute to the patients' symptoms and reduced quality of life, then relief of symptoms becomes the most important goal of treatment.

There are other adverse outcomes that have been associated with anemia in ESKD patients. These include left ventricular hypertrophy, increased risk of death, and an increased number of hospitalizations. It is not possible to determine whether anemia plays a causal role in these outcomes, but for each, it is biologically plausible. However, studies of ESA treatment have failed to demonstrate improvement in these and related outcomes. This has diminished enthusiasm for the prospect of using anemia treatment to improve outcomes, at least with currently available agents.

Anemia Treatments

Erythropoiesis Stimulating Agents

The term *ESA* was developed in anticipation that there would be a variety of different drugs developed that might all be capable of stimulating erythropoiesis. In practice, the term tends to be used for erythropoietin analog drugs. These are glycoproteins produced by recombinant DNA technology that is similar to native erythropoietin in structure and function. The first to be approved was epoetin alfa, followed by other epoetin derivatives and then by darbepoetin alfa and methoxy polyethylene glycol-epoetin beta (Mircera). These biologic originator drugs were followed by biosimilar agents that are currently approved for use in many countries, including the United States.

ESAs work very similarly to native human erythropoietin, stimulating receptors in bone marrow cells to cause red cells to be produced. The U.S. Food and Drug Administration (FDA) suggested a starting dose for epoetin alfa of 50 to 100 units/kg three times per week. Dosing is subsequently adjusted to maintain a target hemoglobin concentration, as discussed later. Darbepoetin alfa has an FDA-recommended starting dose of 0.45 μg /kg every week or 0.75 μg /kg every 2 weeks, and methoxy polyethylene glycol-epoetin beta, 0.6 μg /kg every 2 weeks.

Benefits of Erythropoiesis Stimulating Agent Treatment

The most clearly defined benefit of ESA treatment is a reduction in the need for blood transfusion. This is helpful for several reasons, not the least of which is the logistic problems involved with the large number of blood units required before the introduction of ESAs in 1989. Transfusion of red blood cells is also a source for activation of the immune system or allosensitization. This can increase the difficulty of obtaining a kidney transplant. Moreover, the transfusion blood supply is a critically important resource, and avoidance of large-scale transfusions of the dialysis population is a helpful conservatory step.

Treatment with ESAs in patients with severe anemia has a dramatic effect in reducing anemia-related symptoms. Once a certain level of hemoglobin is reached, the relationship between further increases in hemoglobin and incremental symptom improvement is less well understood. There is a need for individualization based on patients' responses.

Other benefits of ESA treatment have been more difficult to demonstrate. Anemia in dialysis patients is clearly associated with adverse outcomes, including hospitalizations, left ventricular hypertrophy, and even death. Yet, treatment with ESAs has not been consistently demonstrated to result in improvement in any of these outcomes. Most well-powered studies have compared moderate hemoglobin increase to full anemia correction to hemoglobin concentrations in the range of 13–16 g/dL. These studies may not be ideal for addressing the potential to improve outcomes in that any benefit of treatment might have been countered by toxicity of the high ESA doses required. Further studies would be required to determine if more conservative ESA treatment with intermediate hemoglobin target goals could improve some of these important outcomes.

Risks of Erythropoiesis Stimulating Agent Treatment

Since the earliest ESA studies, it has been clear that the most frequent side effect of ESA treatment is an increase in blood pressure. This is particularly important in that hypertension is a cornerstone cardiovascular risk factor and mediator of renal disease progression. Over decades of treatment, it has been recognized that the hypertensive effect of ESAs is rarely a cause for drug discontinuation as it can be readily managed with ESA or antihypertensive dose adjustments.

The more serious risks related to ESA treatment are increases in atheroembolic complications and risk for cardiovascular events. Atheroembolic complications have long been recognized with ESA treatment, including an increase in vascular access clotting noted in the earliest ESA studies from the 1980s. A rapid rise in hemoglobin concentration should be avoided during ESA therapy as one way to reduce clotting risk. In addition, patients with coagulopathies or with recent thrombotic events should be treated especially conservatively.

The cardiovascular risk associated with ESA treatment has only been clearly demonstrated in ESA treatment

studies to high hemoglobin targets (over 13 g/dL). However, and of great concern, these adverse outcomes have been a consistent finding in these studies. The etiology has not been fully elucidated. Observational analyses have found that despite the targeting of high hemoglobin concentrations in these studies, the actual achieved higher hemoglobin tends not to associate with greater cardiovascular risk. This is a puzzle that suggests other possible causal pathways. One other finding from the observational studies has generated considerable interest. That is that higher doses of ESA drugs themselves have correlated closely with adverse cardiovascular risk. Although not proven, the suggestion would be that high doses of these biologic compounds could have negative off-target effects. Accordingly, a more conservative approach to ESA dosing may be justified in patients with a history of cardiovascular disease or at particularly high risk.

Hemoglobin Target Range

With the previous considerations as to the benefits and risks of ESA treatment, a target range for hemoglobin concentration during chronic ESA therapy must be selected. Guideline committees have struggled to an extent to define specific targets that could be widely applied to patients. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines state:

> 3.5.1: In general, we suggest that ESAs not be used to maintain Hb concentration above 11.5 g/dl (115 g/l) in adult patients with CKD.
>
> 3.5.2: Individualization of therapy will be necessary as some patients may have improvements in quality of life at Hb concentration above 11.5 g/dl (115 g/l) and will be prepared to accept the risks.
>
> 3.6: In all adult patients, we recommend that ESAs not be used to intentionally increase the Hb concentration above 13 g/dl (130 g/l).

These statements can be simplified to a hemoglobin target range of 10–11.5 g/dL for most patients. As noted, there may be some patients in which a higher upper end to the target could be employed to achieve greater quality of life benefits. Similarly, we would add that a lower target range might be useful to reduce risk in certain high-risk populations. For example, a target range of 9.5–11 g/dL might be preferred for patients with recent cardiovascular events.

The selected hemoglobin target range is generally utilized by dialysis facilities as part of a standing order that nurses use to make ESA dose adjustments. As hemoglobin results become available, the nurse will use the protocol, often with computer decision support, to either maintain the dose or increase or decrease as necessary. This nurse-driven approach has been found to work well and improve treatment efficiency. However, it does distance the treating nephrologist from ESA therapy details. It is recommended that the nephrologist or other providers do carefully review hemoglobin and ESA dose levels and trends in their patients on a regular and ongoing basis.

Erythropoiesis Stimulating Agent Hyporesponsiveness

A relatively small percentage (10%–20%) of patients treated with ESAs will either occasionally or chronically experience ESA hyporesponsiveness. A definition could be difficulty maintaining hemoglobin > 10 g/dL without use of high ESA doses (we define this as more than 18,000 units per week epoetin alfa, but many definitions exist). Whenever hyporesponsiveness develops, a search for the cause should be undertaken (Table 37.1). Particular care should be taken to check iron status, blood loss, and sources of inflammation.

Iron Management

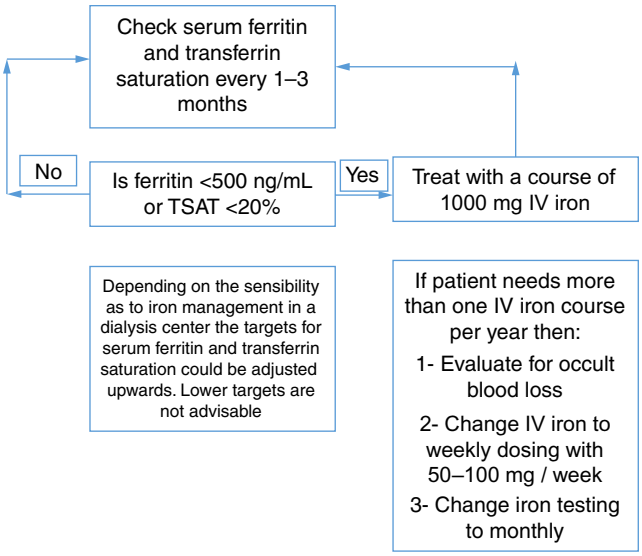
Monitoring of iron status and treatment with IV iron is a core part of ESKD management (Fig. 37.3). The importance of iron in this population is driven by chronic blood loss that makes iron deficiency very common. Treatment with ESA exacerbates the problem by increasing iron needs and further exposing depleted iron stores.

Iron deficiency can be categorized as either absolute or functional. In absolute cases, there is a true whole-body deficiency of iron that is defined as very low or absent iron staining on a bone marrow sample. Among hemodialysis patients, iron-deficient (or restricted) erythropoiesis frequently occurs even when the body has an adequate supply of iron. This has been termed *functional (rather than absolute) iron deficiency*. It reflects an inability to mobilize iron from storage tissues to the developing erythron. It occurs most frequently because of inflammation, which stimulates production of hepcidin (see earlier). This regulator of iron homeostasis responds to inflammation by blocking the release of storage iron into circulation (Fig. 37.4). Functional iron deficiency frequently occurs in hemodialysis patients and often causes the discordant combination of a high serum ferritin (reflecting iron buildup in storage tissues) at the same time as TSAT (reflecting circulating iron) is normal or low.

There is no ideal test of iron status, so most dialysis centers rely on serum ferritin and TSAT as indictors. The tests are performed every 1–3 months, and the results are used to guide iron repletion. No study has been able to link specific results of these tests to a definitive diagnosis of iron deficiency. As a result, clinical judgment is a particularly

TABLE 37.1 Causes of Erythropoiesis Stimulating Agent Hyporesponsiveness

- Inflammation
- Iron deficiency
- Blood loss
- Hyperparathyroidism
- Infection
- Vitamin B_{12} or folic acid deficiency
- Hemolysis
- Other hematologic disorders



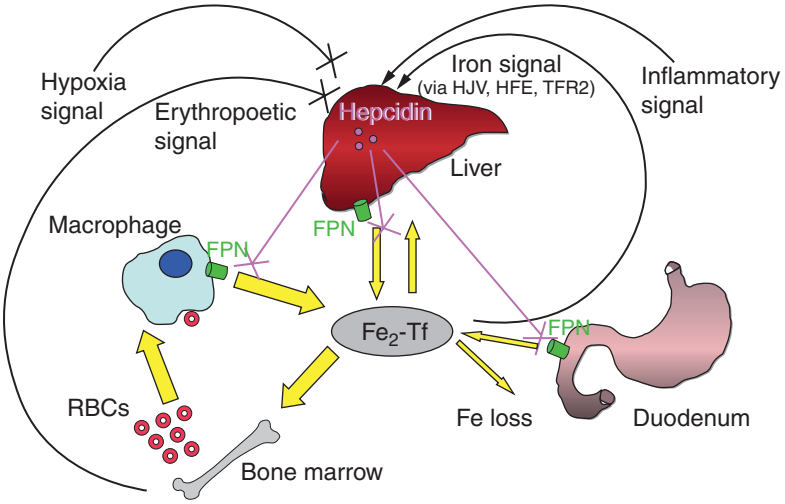
• **Fig. 37.3** Iron Management in Dialysis. During hemodialysis or peritoneal dialysis, iron tests should be checked every 1–3 months. Intravenous *(IV)* iron treatment should be based on test results. We suggest IV iron treatment if the serum ferritin <500 ng/mL or TSAT <20%. Because there is insufficient literature to inform as to the ideal level of these tests, the actual targets can be adjusted for individual patients or in dialysis units with a different sensibility as to IV iron benefits and risks. We generally treat with a course of 10 doses of iron sucrose (1000 mg) in hemodialysis patients (in peritoneal dialysis two to three infusions of 200 mg iron sucrose or a one-time dose of a large dose IV iron drug such as ferumoxytol should be considered). For patients who require repeated courses of IV iron, then regular chronic weekly doses should be administered. In addition, the requirement for repeated series of IV iron should lead to evaluation for sources of occult blood loss. *TSAT*, transferrin saturation.

important aspect of iron treatment decision making. As a general guide to treatment, the KDIGO guidelines state:

> 2.1.3: For adult CKD patients on ESA therapy who are not receiving iron supplementation, we suggest a trial of IV iron … if an increase in Hb concentration or a decrease in ESA dose is desired and TSAT is ≤30% and ferritin is ≤500 ng/ml.

It is interesting to note that at the time of this writing, the mean serum ferritin among U.S. hemodialysis patients is approximately 750 ng/mL. Since the KDIGO guideline calls for treatment when ferritin is less than 500 ng/mL, it is clear that clinical practice has followed a more aggressive path. It is likely that the motivating factor for increased use of IV iron is to cause a reduction in ESA dose requirement for financial and safety reasons. Many studies have found that IV iron treatment results in reduced ESA dose requirements.

Treatment with iron is generally administered by the IV route in both hemo- and peritoneal-dialysis patients (Table 37.2). Randomized controlled trials have found that traditional oral iron supplements lack efficacy, especially in hemodialysis patients. In published studies, oral iron has had no greater efficacy than placebo or no iron treatment study groups. As a result, IV iron is preferred. One exception is the oral iron agent ferric citrate. This drug is approved by the FDA for dialysis patients for use as a phosphate binder. But as it binds phosphate, it also releases iron that is absorbed into the circulation. Umanath et al. found the drug to be an effective means for iron supplementation in dialysis patients while used as a phosphate binder. Subsequent studies led to



• **Fig. 37.4** Hepcidin is the body's master regulator of iron status. Excess iron causes hepcidin release by the kidney, which then causes blockage of iron absorption from the intestines and iron release from storage tissues. Iron deficiency leads to a reduction in hepcidin and greater iron availability. Hepcidin release is stimulated not just by iron overload but by inflammation as well. As a result, when inflammation is present, iron tends to be less available. In patients with end-stage kidney disease, this is important since inflammation is commonly present. This limits iron availability and contributes to the frequent occurrence of functional iron deficiency. *Fe_2-Tf, iron and transferrin; FPN,* ferroportin; *HFE, hemochromatosis gene; HJV,* hemojuvelin; *RBC,* red blood cell; *TFR2,* transferrin receptor 2. (From Babbitt JL, Lin HY. Molecular mechanisms of hepcidin regulation: implications for the anemia of CKD *Am J Kidney Dis*. 2010;55(4):726-741.)

TABLE 37.2 Intravenous Iron Preparations for CKD patients

Name	Initial U.S. FDA Approval	Maximum Single Dose	U.S. FDA Black Box Warning
Iron dextran (Infed)	1974	100 mg	Yes, risk for anaphylactic-type reactions including fatalities
Sodium ferric gluconate complex (Ferrlecit)	1999	125 mg	No
Iron sucrose (Venofer)	2000	HD: 100 mg PD: 300 or 400 mg	No
Ferumoxytol (Feraheme)	2009	510 mg	Yes, risk for serious hypersensitivity/ anaphylaxis reactions
Ferric carboxymaltose (Injectafer) (nondialysis CKD)	2013	≥50 kg: 750 mg <50 kg: 15 mg/kg	No
Ferric derisomaltose (Monoferric) (nondialysis CKD)	2020	≥50 kg: 1,000 mg <50 kg: 20 mg/kg	No

CKD, Chronic Kidney Disease; *HD*, hemodialysis; *PD*, peritoneal dialysis; *U.S. FDA*, US Food and Drug Administration.

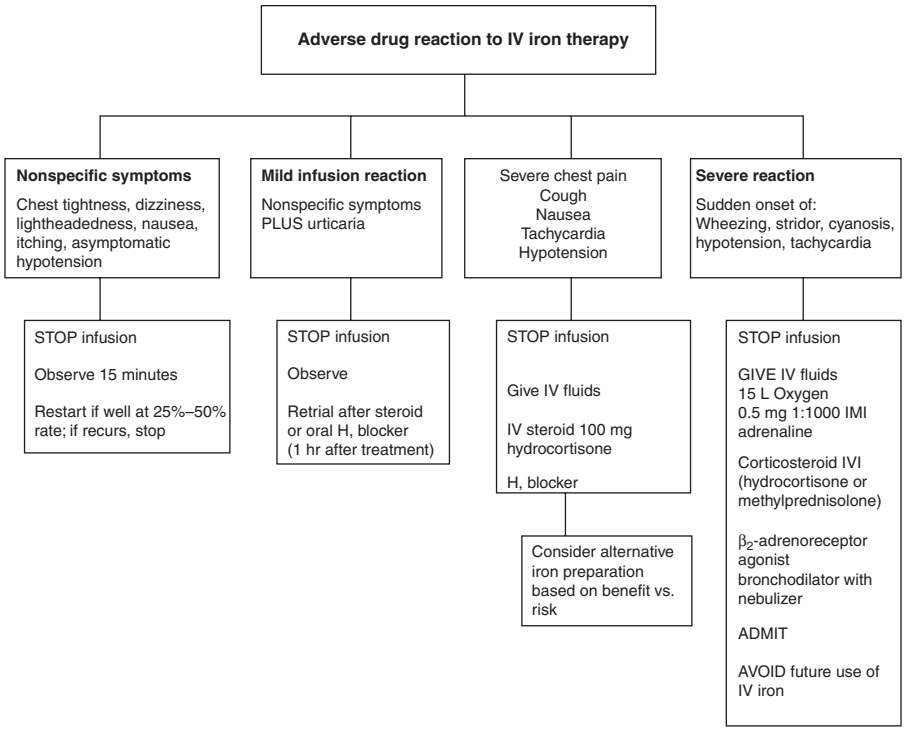
the drug receiving an FDA indication for treatment of iron deficiency anemia in nondialysis CKD.

IV iron has consistent efficacy and a reasonable safety profile. Occasional patients will experience some degree of reduction in blood pressure or very rarely a severe acute reaction. All facilities must be prepared for treatment of these occasional reactions (Fig. 37.5). Observational studies have suggested the possibility of cardiovascular toxicity or increase in infection risk with chronic use. A well-powered randomized controlled trial authored by Macdougall et al. studied IV iron safety. The comparison was between proactive and intensive IV iron treatment (400 mg monthly, unless the ferritin concentration was >700 µg/L or the TSAT was ≥40%), or very conservative treatment where the drug was administered only if ferritin was <200 µg/L or TSAT <20%. The study found that the more aggressive approach to IV iron therapy was not associated with an increase in any adverse outcomes. Although not definitive, the study provides a degree of reassurance in the general safety of IV iron therapy.

Role of Red Blood Cell Transfusion in Management of Anemia of End-Stage Kidney Disease

While ESAs remain the main treatment option in the management of anemia of ESKD, the use of red blood cell transfusion in this population has recently increased in the United States. This increase in transfusion and decrease in ESA utilization among U.S. long-term dialysis patients may be a result of ESA-related safety concerns and major ESKD-related regulatory and reimbursement changes. In any case, transfusion of packed red blood cells should be considered in ESKD patients who are experiencing symptoms related to severe anemia and in patients with acute bleeding. Red blood cell transfusion also needs to be considered in chronically anemic ESKD patients in whom ESA therapy has been insufficiently effective (as a result of bone marrow failure, hemoglobinopathies, or ESA resistance) or when the risks of ESA therapy outweigh its benefits. The KDIGO Anemia Work Group suggests the use of red blood cell transfusions in patients in whom urgent correction of anemia is required to stabilize the clinical condition (for example, in cases of acute hemorrhage, unstable coronary artery disease) or when rapid preoperative hemoglobin correction is required.

Both benefits and risks of red blood cell transfusions should be considered in this patient population. The clinical benefit of red cell transfusion primarily includes rapid improvement in symptoms related to anemia. Although uncommon, several risks that are associated with red blood cell transfusions should be considered in a given ESKD patient. These include volume overload, hyperkalemia, citrate toxicity (causing metabolic acidosis and hypocalcemia), hypothermia, coagulopathy, and immunologic reactions, including transfusion-related acute lung injury (TRALI). Although rare, transmissions of infections remain a concern with red blood transfusion. Another important concern, although disputed, is the risk of allosensitization and resulting diminished subsequent ability to receive a kidney transplantation. Hence, to minimize the risk of allosensitization, especially in patients who are candidates for kidney transplantation, the KDIGO guidelines suggest avoiding red blood cell transfusions in chronically anemic CKD patients when possible. For the previously mentioned reasons, red



• **Fig. 37.5** Suggested Management of Reaction to IV Iron Injections. *IV*, Intravenous. (From Macdougall IC, Bircher AJ, Eckardt KU, et al. Iron management in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2016;89(1):28-39, 34.)

blood cell transfusions should be used prudently in chronically anemic ESKD patients.

Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors

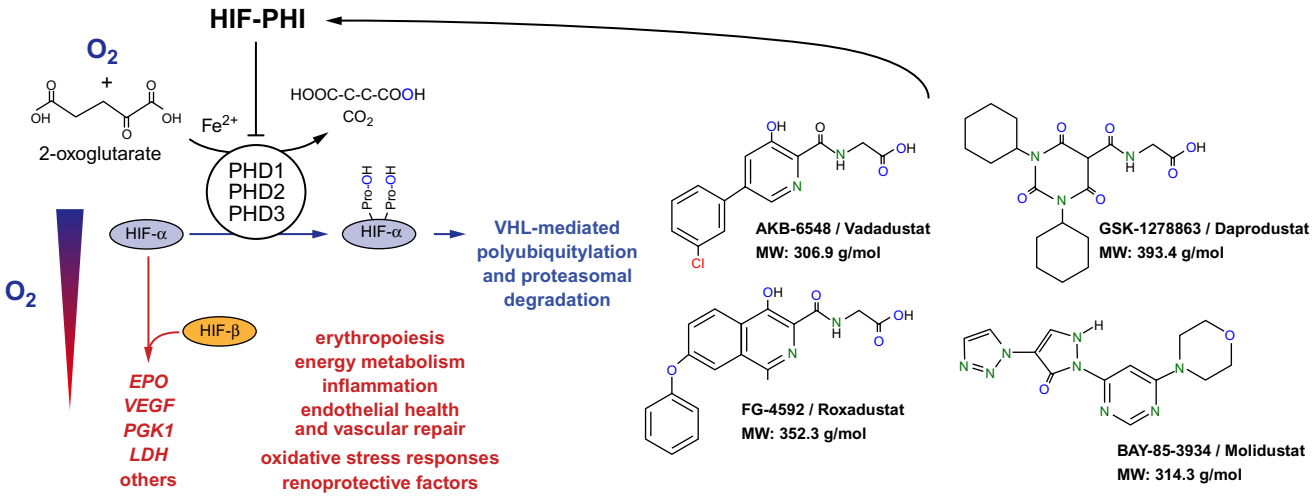
A new class of anemia treatment drugs for patients on dialysis is the HIF prolyl-hydroxylase inhibitors (PHIs). These are oral agents, unlike ESAs, which are all injectable. They work through their effect in the body's oxygen sensing and hypoxia protection system (Fig. 37.6).

The key mediators in the oxygen sensing system are HIFs and HIF prolyl hydroxylases (PH). The latter are enzymes that sense ambient oxygen. When oxygen is sufficient, the PHs add hydroxyl groups (-OH) to proline residues on HIF. This reaction marks the HIFs for degradation, which rapidly occurs. In contrast, if hypoxia is present, then the PHs are inhibited, and HIFs are not degraded. This stabilization of HIFs leads to their moving to the cell's nucleus, where they stimulate the production of a large number of gene products that work to protect cells from hypoxia. One of these proteins is erythropoietin, which serves a adaptive protective role in hypoxic conditions by stimulating the production of new erythrocytes to carry oxygen. Recent advances in the understanding of HIF biology led to exploration and research into the potential for drugs that block the PHs, leading to the oral HIF-PHIs (Fig. 37.6).

The HIF-PHIs work to treat anemia in CKD by several mechanisms. The most proximate effect is an increase in serum erythropoietin. The second effect is increased production of a number of proteins involved in iron balance, such as transferrin, divalent metal-ion transporter 1, ceruloplasmin, ferroportin, and indirect downregulation of hepcidin. The net effect is improved iron absorption in the intestines, increased iron mobilization from storage macrophages, and overall increased iron availability for erythropoiesis. Taken together, these changes could result in a decrease in the need for IV iron treatment for patients on dialysis.

Three HIF-PHI drugs are in the final stages of development at the time of this writing; roxadustat, vadadustat, and daprodustat in the United States. All work to inhibit HIF-PHs, allowing HIF to be stabilized. Phase 2 study results have been published for each of these agents. Results indicated that serum erythropoietin levels were increased sufficiently to induce erythropoiesis, but not to the very high levels found after injection of ESAs. To the extent that high ESA doses and the resultant surges in serum erythropoietin levels may be related to ESA cardiovascular toxicity (see earlier), this more moderate increase in serum erythropoietin may be a helpful property of the HIF-PHIs. The phase 2 studies also indicated increases in hemoglobin to the therapeutic range, improved iron availability, and an early sense that the drugs were well tolerated.

If these drugs are established to have sufficient safety, then approval by regulatory agencies may be expected. The



• **Fig. 37.6** The Hypoxia-Inducible Factor *(HIF)* System and Agents That Can Stimulate It. The blue ovals show HIF-alpha, which with HIF-beta are the keys molecules that affect the cells response to hypoxia. When sufficient oxygen is present, it can be seen in the upper part of the figure that HIF is degraded. The sensing of oxygen tension is by prolyl hydroxylases (PHs), which mark HIF for inactivation when normal oxygen conditions exist. If hypoxia occurs, as can be seen on the lower section of the figure, HIF is not degraded. Instead, it interacts with genes that lead to the production of molecules that protect the cell from hypoxia. As can be seen on the figure, some of the molecules are erythropoietin *(EPO)*, vascular endothelial growth factor *(VEGF)*, phosphoglycerate kinase 1 *(PGK1)*, lactate dehydrogenase *(LDH)*, and many others. The drugs, prolyl hydroxylases (PHIs), seen on the right side of the figure, block the PHs, and thereby stabilize HIF. *PHD*, prolyl hydroxylases domain; *PHI*, prolyl hydroxylases inhibitor; *VHL*, von Hippel-Lindau. (From Sanghani NS, Haase VH. Hypoxia-inducible factor activators in renal anemia: current clinical experience. *Adv Chronic Kidney Dis*. 2019;26(4):253-266.)

fact that the HIF-PHIs are administered orally would clearly be favorable for patients on peritoneal dialysis and patients with nondialysis CKD. Use among hemodialysis patients is likely to depend on differential safety factors, if any, and financial factors.

Recommended Reading

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Resistance to Erythropoiesis Stimulating Agent (ESA) Treatment

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Anemia is a well-known complication of chronic kidney disease (CKD); its severity increases as renal function declines, with nearly 80% of patients on dialysis having a certain degree of anemia.

Although the pathogenesis of anemia is multifactorial, it is primarily caused by an erythropoietic hypoproliferative state due to relative insufficiency of erythropoietin (EPO) production from the failing kidneys. This complex pathophysiological context forms the basis for why the severity of the anemia and its response to treatment is highly heterogeneous at a given stage of CKD and is not often predictable in everyday clinical practice.

Since the late 1980s, the use of erythropoiesis-stimulating agents (ESAs) has revolutionized the management of renal anemia, significantly improving patient quality of life and reducing the need for blood transfusions. In general, ESAs are effective agents and increase hemoglobin (Hb) levels in a dose-dependent way. However, maintaining patients at Hb levels that are both safe and provide maximal benefit is a continuing challenge. Moreover, despite the general efficacy of ESAs, ~5%–10% of patients exhibit an inadequate response. In this setting, the definition of ESA hyporesponsiveness/resistance has been introduced to identify the inability to achieve or maintain target Hb levels despite higher than usual doses of ESAs.

Definition of Hyporesponsiveness/ Resistance to Erythropoiesis Stimulating Agents

The identification of patients with low responsiveness to ESAs is important for clinical and economic reasons. However, no standardized definition has been produced over the last three decades. In this respect, it should be emphasized that the concept of the optimal Hb to target with ESAs has progressively evolved over the years, together with the knowledge of possible safety risks with ESA use at high doses. For this reason, the understanding and definition of ESA hyporesponsiveness have evolved as well. What was accepted 15 years ago as the maximal ESA dose is not necessarily accepted today. However, the general concept has remained unchanged: a patient is hyporesponsive to ESAs when his dose requirements to either achieve or maintain a desired Hb level are higher than expected according to CKD stage, clinical characteristics, and geographical area.

Looking back, in the 1990s or early 2000s, available international guidelines on anemia treatment proposed their own definition.

According to the Revised European Best Practice Guidelines (EBPG), which were published in 2004, ESA hyporesponsiveness was defined as a failure to attain the Hb target concentration while receiving more than 300 IU/kg/week (> 20,000 IU/week) of epoetin or 1.5 μg/kg of darbepoetin alfa (> 100 μg/week) or has a continued need for such high dosages to maintain the target. This is > 2.5 times the average ESA dose, so most (> 90%) iron-replete patients given ESAs would be expected to respond to a lower dose. At that time, methoxy polyethylene glycol-epoetin beta was not available in the market yet and thus was not included in the definition.

In 2012, Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines defined ESA hyporesponsiveness as:

1) A significant increase in the ESA dose requirement to maintain a certain Hb level or a significant decrease in Hb level at a constant ESA dose.
2) A failure to increase the Hb level to greater than 11 g/dL despite an ESA dose equivalent to epoetin greater than 500 IU/kg/wk.

ESA hyporesponsiveness can be observed even at treatment start. Alternatively, higher dose needs can be seen after months or years of optimal response. This evolving clinical scenario was taken into consideration by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines in 2012. They classified ESA hyporesponsiveness as "initial" (if there is no increase in Hb concentration from baseline after the first month of ESA treatment on appropriate weight-based dosing) or "subsequent" (if there is a need for two increases in ESA doses up to 50% beyond the dose at which the patient had been stable in order to maintain a stable Hb level).

Since a < 2% increase in the Hb concentration is likely to be within the variability range of Hb values in individual patients, this value was set as "no increase." Differing from previous guidelines, the concept of a maximal dose to define hyporesponsiveness or resistance has disappeared. This has a number of implications from the practical point of view. Indeed, the definition of hyporesponsiveness was developed following the evidence coming from the Trial to Reduce cardiovascular Events with Aranesp Therapy (TREAT) study. This was a prospective, double-blind, randomized controlled trial of darbepoetin alfa versus placebo for the treatment of anemia in 4038 participants with type 2 diabetes mellitus, CKD not on dialysis, and anemia (Hb < 11.0 g/dL). The initial dose of darbepoetin alfa in the active treatment arm was 0.75 μg/kg, with doses adjusted monthly according to a computer-based algorithm to target Hb at 13 g/dL. The administration frequency was every 2 weeks. If lower initial dosages than those used in TREAT are chosen, the diagnosis of hyporesponsiveness must take this into account, and repeated escalations in ESA dose should be allowed to reach double the weight-based dose used in TREAT (i.e., two 50% dose escalations) starting from the TREAT initial dose.

Another point to be considered is that the TREAT study was performed in a population of patients with diabetes (and thus possibly with higher ESA dose needs) with CKD, not on dialysis. Interestingly, a post hoc analysis of TREAT showed that Hb declined precipitously in the year prior to the development of end-stage kidney disease (ESKD) (on average 1.15 g/dL lower in those who developed ESKD versus those who did not) with simultaneous increase in the mean darbepoetin dose (15% higher than those not reaching ESKD). Considering that hemodialysis (HD) patients have, on average, higher dose needs than patients not on dialysis, a higher setpoint has to be possibly considered.

In general, in order to fulfill the definition of ESA hyporesponsiveness, the patient has to be iron replete. Even if this could appear simple at first sight, looking more in depth, it is not necessarily easy to rule out this point. Indeed, many patients who are hyporesponsive to ESAs are inflamed and experience functional iron deficiency (i.e., high ferritin levels but low transferrin saturation [TSAT]).

The response to ESAs is made by the relationship between the desired Hb and ESA needs; this relationship is complex, nonlinear, and dynamic. In order to mathematically represent this concept, the ESA resistance index (ERI) has been proposed. This is the ratio between average weekly EPO dose (IU) (or other ESA molecules) per kilogram of body weight divided by Hb (g/dL). Considering the nonlinear and dynamic kinetics of Hb response to ESAs and that Hb has its own variability, the use of average values over at least a 3-month period is suggested. Indeed, in a moving 3-month window, ERI varies over time as Hb increases in response to the constant ESA dose. ERI is generally used for research purposes, and it is not commonly used in everyday clinical practice. However, some authors proposed its use as a useful tool to guide dosing; when elevated, ERI could trigger an evaluation for remediable factors causing hyporesponsiveness, even when Hb goals have been reached. However, ERI has the limitation of not taking into account iron stores or availability.

Epidemiology of Hyporesponsiveness to Erythropoiesis Stimulating Agents

The true incidence of ESA hyporesponsiveness is still a matter of study, and probably, it differs among countries (in the United States, it is likely to be higher than in Europe and even higher again than in Japan). Also, the lack of a universally accepted definition influences the high variability of estimates.

It is well known that, on average, ESA dose requirements differ among countries, reflecting a different burden of comorbidities (higher in the United States), possible differences in age, gender, race, ethnicity, and body mass index, dialysis vintage, treatment practices, and reimbursement policies. These differences are clearly shown by the Dialysis Outcomes and Practice Patterns Study (DOPPS). This is a prospective cohort study of HD practices based on the collection of observational longitudinal data for a random sample of patients from dialysis facilities in a representative and random sample of units in 20 countries. Patients from Japan, France, and Italy had been on dialysis significantly longer. The body mass index was significantly lower in Japan and significantly higher in the United States. More patients in Canada and the United States had diabetes. ESA doses and the percentage of patients with a weekly ESA dose > 35,000 IU/week were highest in the United States (18.1%). In European countries, this percentage ranged from only 1.8% in Germany to 12.7% in Sweden. In Japan, no patients received these high treatment ESA doses. These figures are partially influenced by reimbursement policies that were in place at the time of data collection in the different countries. Indeed, ESA reimbursement was often limited to a maximum dose applying not necessarily to all the ESA molecules.

The prevalence of ESA hyporesponsiveness in HD patients has been reported between 7.3% and 17.6%. However, a small cross-sectional study of 550 Italian HD patients reported a much lower percentage (only 2.4% when using the EBPG definition of ESA hyporesponsiveness) due to iron deficiency in many cases. Conversely, the prevalence of hyporesponsiveness to ESAs was much greater in a cohort from a large dialysis organization (DaVita) in the United States (43% of the patients received more than 18,000 IU/week of epoetin). However, these estimates did not discriminate between chronic and acute (and therefore reversible) ESA hyporesponsiveness. Indeed, taking this difference into consideration and using three definitions of hyporesponsive dialysis patients (total ESA dose, ESA dose per kg of body weight, or ESA dose per Hb level), Gilbertson et al. showed a prevalence of 4.5%, and 15% of patients with chronic and acute ESA hyporesponsiveness, respectively.

According to this estimate, 50% of total ESA costs were spent on the 15% of patients requiring the highest dosage.

Clinical Use of Erythropoiesis Stimulating Agents in Hyporesponsive Patients

All ESAs are effective in correcting renal anemia and increasing Hb levels. However, ESAs differ in amino acid sequence, carbohydrate content, charge, and molecular weight. These characteristics influence their half-life and biological activity and, thus, their clinical use in hyporesponsive patients. Indeed, the higher the molecular weight and the carbohydrate content, the longer the half-life and the lower the affinity to the EPO receptor. Epoetin alfa and beta behave similarly with a half-life of nearly 8 hours when administered intravenously and of 24 hours for the subcutaneous route. Darbepoetin alfa has a half-life of 25 and 48 hours when given intravenously and subcutaneously, respectively. Methoxy polyethylene glycol-epoetin beta has a half-life of nearly 130 hours, which is independent of the administration route.

According to pharmacokinetics/pharmacodynamics characteristics, less frequent dosing of ESAs is more effective for the molecules with longer half-life (i.e., darbepoetin alfa or methoxy polyethylene glycol-epoetin beta) or in patients not on dialysis. However, the labels of all the different ESA molecules allow delayed administration frequencies. However, patients with high dose requirements are less likely to benefit from less frequent administration of short-acting ESAs. Indeed, several studies have shown that this strategy is effective without the need for extradosing, mainly in patients with low dose requirements. In hyporesponsive patients, administering a short-acting ESA at a low frequency implies very high serum peaks, potentially exposing them to ESA-related adverse events. It also implies extra costs. For this reason, it is reasonable to suggest in hyporesponsive patients that administration frequencies should respect as much as possible the original recommendations based on the pharmacokinetics of every single agent.

It has been suggested that at high doses, long-acting ESAs may have a more favorable conversion factor from epoetin alfa and beta, possibly reflecting different kinetics in the activation of the EPO receptor. However, this has not received definitive confirmation from the scientific community.

Recently, a large cohort study from the Japanese Registry of Dialysis compared the mortality risk associated with the use of short-acting versus long-acting ESAs. According to crude data analysis, the long-acting ESAs were associated with a 20% higher risk of all-cause death than short-acting ESAs. Of interest for this chapter is the fact that the difference in risk was higher among patients receiving high ESA doses and those who had high ERI. Long-acting ESA use was also associated with an increased rate of death from cardiovascular diseases, infection, and malignancies. Darbepoetin alfa users had the highest rate of all-cause death, death from cardiac diseases, and malignancies. Despite several strengths, this study also has several limitations. In particular, despite the large sample size and similar baseline characteristics between long- and short-acting ESA users, potential prescription biases at patient and facility level and residual confounders cannot be ruled out. A large amount of missing data on ESA type, major covariates, and TSAT may have influenced patient selection and adjusted analyses. Interestingly, the study showed that the outcomes of ESA users might be different for achieved Hb levels. Indeed, for achieved Hb levels < 11 g/dL, long-acting ESA users had a slightly higher risk of all-cause death compared to those treated with short-acting agents; no difference was found for higher achieved Hb values. Of note, in Japan, there is a maximum reimbursable dose for short-acting ESAs of 9000 units per week (determined from prescribing information on the ESA label). This may account for a possible prescription bias toward a higher use of long-acting ESAs in hyporesponsive patients.

In the same period, a large, randomized study aimed at comparing postapproval safety of methoxy polyethylene glycol-epoetin beta in comparison to reference ESAs did not confirm a different safety profile among ESA molecules with respect to the risk of major adverse cardiovascular events or all-cause mortality.

Another concept to be kept in mind is that dose requirements of long-acting ESAs are similar either subcutaneously or intravenously. On the contrary, short-acting ESAs have, on average, a 30% extra dose requirement when administered intravenously. This difference is important, considering that now, virtually all HD patients receive ESAs intravenously.

ESA dose requirements are hard to predict in individual patients. However, patients with comorbidities, diabetes, cardiovascular disease, and inflammation are more likely to have high dose needs. The role of body weight and obesity is still controversial, with some studies showing lower per-kilo dose requirements in obese patients. According to an analysis of the national database of the DaVita dialysis organization on 38,328 prevalent HD patients, low iron stores, hyperparathyroidism, and high-turnover bone disease, together with lower estimated dietary protein intake and signs of malnutrition, were associated with a greater risk of ESA hyporesponsiveness.

At present, there is an agreement to avoid the use of excessively high ESA doses. How this recommendation should be translated into clinical practice is less clear. In 2010, the European Renal Best Practice (ERBP) position statement gave generic suggestions to balance increased cardiovascular risk with the possible benefits of anemia correction obtained with high ESA doses. In particular, dose escalation should be avoided in those patients who do not respond to treatment or in whom it is obvious that worsening of anemia is linked to nonrenal factors. Risks and benefits should also be carefully evaluated in patients with cancer in whom cure is an anticipated outcome.

In 2015, National Institute for Health and Care Excellence (NICE) guidelines confirmed the recommendations that were given in 2006, focusing on a balance between the pros and cons of a trial of anemia management to be discussed among the clinician, the person with anemia of CKD, and their families and caregivers if applicable. Consideration to not administer ESAs may be appropriate in the presence of comorbidities or when the prognosis is likely to negate the benefits of correcting the anemia. As an alternative, a trial with ESAs could be tried in the presence of uncertainty over the benefit of correcting with ESAs. When appropriate, ESA withdrawal should be considered.

KDIGO guidelines on anemia therapy, which were issued in 2012, also reported a number of recommendations about avoiding excessive ESA dose escalation in those who are either hyporesponsive at treatment start or those who become later on. Unfortunately, these recommendations are all issued starting from a low degree of evidence and thus are either not graded or are graded 2D at maximum. In particular, it is suggested to avoid repeated escalations in ESA dose beyond double the initial weight-based dose (initial hyporesponsiveness, 2D) or beyond double the dose at which the patient had been stable (acquired hyporesponsiveness, 2D). If a patient remains hyporesponsive despite correcting treatable causes, KDIGO suggests individualizing further anemia therapy after having balanced its pros and cons. Among possible options, physicians can decide to keep the patient at a lower Hb level, to continue a high ESA dose, and/or give blood transfusions when needed.

Hyporesponsiveness and Outcomes

Hyporesponsiveness to ESAs has been clearly associated with adverse outcomes in HD or nondialysis CKD patients. The gathering of this knowledge comes from either observational studies or secondary analyses of randomized clinical trials. According to a retrospective cohort study of 128,598 HD patients, there is a dose-dependent positive association between weekly epoetin-α doses ≥18,000 U/week and mortality risk. Similar findings were shown by a cohort study with data obtained from Clinical Research Center registry for ESKD in Korea. In this population of 1594 prevalent HD patients, those with high-dose ESAs and low Hb levels had a significantly higher risk of all-cause mortality in comparison with those with a better response to ESA therapy.

Similarly, using data from the U.S. Renal Data System, Zhang et al. found that epoetin requirements predict mortality in a large cohort of prevalent HD patients (n = 94,569). In particular, for every hematocrit cohort studied, patients administered higher doses of epoetin had significantly lower hematocrit values and greater mortality rates; a significant nonlinear relationship between increased epoetin dose and mortality was also found regardless of hematocrit, with the steepest increase in relative risk for death in the 25th higher percentile.

The RISCAVID ("RISchio CArdiovascolare nei pazienti afferenti all'Area Vasta In Dialisi") was an observational study, which was performed in Tuscany, Italy, between 2004 and 2007. Among a population of 651 prevalent HD patients receiving ESAs, quartiles of ERI correlated with all-cause mortality and fatal/nonfatal cardiovascular (CV) events, with those in the highest quartile having the highest risk.

Looking at randomized clinical trials, already back in the nineties, Besarab et al. showed that the patients who did not achieve a given Hb target have a higher risk of death. In this randomized clinical trial, 1233 HD patients with clinical evidence of congestive heart failure or ischemic heart disease were assigned to either a lower (30%) or higher (42%) hematocrit during therapy with epoetin alfa. In both the randomization groups, the mortality rate in each group at various hematocrit values, calculated as the average of all values until death, loss to follow-up, or study end, increased at lower hematocrit values. Using a Cox multivariate analysis, a 30% decrease in the risk of death or myocardial infarction was shown per 10-point increase in average hematocrit. Unexpectedly, a higher epoetin dose was not associated with increased mortality.

More recently, the secondary analysis of a recent, randomized postmarketing study aimed at comparing postapproval safety of methoxy polyethylene glycol-epoetin beta in comparison to reference ESAs showed that the patients with a 3-month average Hb of < 10 g/dL (i.e., those who did not achieve the Hb target of the study despite ESA therapy) had a threefold higher risk of experiencing a primary endpoint compared with the reference category (10–11 g/dL).

It is still matter of debate whether high ESA doses may cause damage or hyporesponsiveness to ESAs is just a marker of increased comorbidities.

It is well known that, in addition to erythropoiesis stimulation, ESAs have a number of pleiotropic effects in several tissues where the EPO receptor is expressed. Some of them may be beneficial, but others could be harmful, especially at high ESA doses. This would suggest a possible negative effect of excessive ESA doses per se.

However, as shown by a secondary analysis of the TREAT study, the predictive role of ESA response on patient outcome seems to be present already at treatment start. Indeed, the subgroup of patients who demonstrated an Hb change of < 2% after 1 month following a fixed starting dose of darbepoetin alfa (i.e., those having an initial poor response) had a higher risk of reaching the cardiovascular composite endpoint than the better Hb responders (who had an event rate similar to the placebo group). Even if this does not exclude a negative effect of exposure to higher ESA doses, it may suggest that preexisting inflammation or comorbidities are of more importance. Accordingly, these patients were more likely to have previous cardiovascular disease or receive treatment for heart failure, have higher C-reactive protein (CRP) levels, and be overweight. Interestingly, ESA hyporesponsiveness has been linked to insulin resistance, which is more likely to occur in overweight patients and is a well-known cardiovascular risk factor.

Some years ago, Gillespie et al. performed a case-crossover study on a cohort of 6645 European CKD HD patients and evaluated the reversibility of ESA hyporesponsiveness and the factors associated with the transition to this state. ESA responsiveness was defined on the basis of the median dose threshold. Transition to hyporesponsiveness was associated with hospitalization, vascular access changes, or worsening inflammation, with these factors accounting for over two-thirds of transitions. Clear causes or risk factors of hyporesponsiveness could be identified in 68% of the patients. In the remaining ones, hyporesponsiveness remained unexplained. The fact that the identified factors were independent risk factors for poorer outcomes is a further confirmation that ESA hyporesponsiveness is a risk marker rather than a risk factor.

Causes of Hyporesponsiveness and Their Management

The pathogenesis of the anemia related to ESA resistance can be attributable mainly to three mechanisms: iron-restricted erythropoiesis, inflammation, and bone marrow suppression. The relationship of one with the other is complex, but very often, they are closely interwoven. Bearing this concept in mind, many of the risk factors that have been described as causes of ESA hyporesponsiveness can be ascribed to these three mechanisms (Box 38.1). In particular, the development of iron deficiency or the occurrence of an inflammatory state is very common. In this regard, intercurrent infections are the most frequent reason why patients become temporarily (and reversibly) ESA-resistant.

Occult blood loss, severe hyperparathyroidism, malnutrition, and inadequate dialysis are also important. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists may play a role in some instances. Compliance should also be checked in patients self-administering an ESA.

Some causes of ESA resistance are little evident; their identification requires an in-depth diagnostic workout. As suggested by KDIGO guidelines, patients with either initial or acquired ESA hyporesponsiveness should be evaluated and then treated for specific causes of poor ESA response (Not Graded).

Unfortunately, as shown by Gillespie et al. in an observational study, one-third of the patients have no identifiable cause.

• BOX 38.1 Possible Causes of ESA Hyporesponsiveness

Absolute iron deficiency	Aluminum intoxication
Functional iron deficiency	Uremic toxins
Inflammation	Malignancies
Infections	Bone marrow disorders
Lack of dialysis adequacy	Pure red cell aplasia
Malnutrition	Severe hyperparathyroidism
Low 1,25-dihydroxyvitamin D level	Hemolysis or hemoglobinopathies
Use of myelosuppressive agents	Occult bleeding
Use of ACEIs/ARBs	Specific nutritional factor deficiencies
Continued Hospitalization	Central vein catheter insertion
Chronic rejection	Gut microbiota dysbiosis

ACEI, Angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptor blocker; *ESA*, erythropoiesis stimulation agent.

Iron Deficiency

This is by far the most frequent cause of ESA hyporesponsiveness. Iron deficiency could be absolute or functional. Among HD patients, absolute iron deficiency is defined when TSAT is $\leq 20\%$, and the serum ferritin concentration is ≤ 200 ng/mL.

Even in recent years, the attention of the scientific community has focused more on very high ferritin levels and the connected risk of iron overload, data from the DOPPS Practice Monitor, show that nearly 8% of patients have ferritin levels below 200 ng/mL.

In the case of ESA hyporesponsiveness, low ferritin levels must be corrected with intravenous (IV) iron administration. This is particularly true in the light of the finding of the Proactive IV Iron Therapy in Haemodialysis Patients (PIVOTAL) trial, which showed that high-dose IV iron sucrose given proactively (400 mg monthly, unless ferritin was >700 µg/L or TSAT $\geq 40\%$) was superior to a lower dose of IV iron sucrose given in a reactive fashion (0 to 400 mg monthly if ferritin was <200 µg/L or TSAT <20) in reducing the risk of reaching the composite primary endpoint (nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or death). Moreover, the proactive regimen led to significantly reduced ESA doses during follow-up. Of note, the applicability of these findings to hyporesponsive patients could be limited, since according to the design of PIVOTAL, enrolled patients had a short dialysis vintage and little signs of inflammation.

Even if absolute iron deficiency is among the possible causes of ESA hyporesponsiveness, functional iron deficiency is by far more common. This state is characterized by reduced iron availability for erythropoiesis despite its presence within the storage sites. There is not a univocal accepted definition for functional iron deficiency differing from absolute iron deficiency; in general, its presence is suggested by the coexistence of low TSAT together with normal or high serum ferritin levels. Even if the mechanisms of iron sequestration are not

completely understood, it is well accepted that hepcidin and inflammation have an important role, with inflammation increasing the hepatic production of serum hepcidin, which in turn reduces iron absorption from the gut and its mobilization from the reticulo-endothelial system and hepatocytes because of the action of hepcidin on ferroportin. Given that free iron is an important substrate for the replication of many bacteria, this likely reflects an ancestral mechanism of defense for the body against infections. Looking at the more recent data from the DOPPS Practice Monitor (October 2019), it is notable that nearly one-fourth of the patients have TSAT values less than 20%, and nearly half have serum ferritin ≥ 800 ng/mL. This clearly suggests that a significant subset has the coexistence of low TSAT levels and very high ferritin levels. Of note, in some cases, high ferritin values are associated with hyporesponsiveness with no relationship with TSAT, being in that case simply an inflammatory marker.

Given that functional iron deficiency is generally the consequence of an inflammatory state, it cannot be considered a true cause of ESA hyporesponsiveness per se. However, cautious use of IV iron could be considered in selected cases. In 2007, the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) trial evaluated the efficacy of IV ferric gluconate in patients with functional iron deficiency and high ESA dose needs (Hb ≤ 11 g/dL, ferritin 500 to 1200 ng/mL, TSAT ≤ 25%, and epoetin dosage ≥ 225 IU/kg per week or ≥ 22,500 IU/week). It showed that the patients who received a trial of 125 mg of ferric gluconate intravenously for eight dialysis sessions obtained significantly higher Hb levels at week 6 than those in the control group without any significant safety issues. Unfortunately, the efficacy and safety of this therapeutic strategy have not been verified by long-term studies. Moreover, high-dose IV iron could be harmful in patients with iron deficiency for several reasons. First, it could cause iron overload, as shown by several studies performed in HD patients with high ferritin levels. Second, in the presence of a state of an inhibition of iron uptake, free iron could contribute to oxidative stress and direct cell damage. Finally, free iron could have a possible contributory role in accelerating atherosclerotic processes.

Inflammation

Chronic inflammation is a major cause of hyporesponsiveness to ESAs. Indeed, the link between anemia and inflammation is well known since it produces the so-called anemia of chronic disease. Anemia of chronic disease is usually a mild or moderate condition, but when added to anemia of CKD, it can worsen it significantly and increase ESA dose needs. It is characterized by a microcytic or normocytic anemia and low reticulocyte count. Values for serum iron and transferrin are typically low to normal, while the serum ferritin value can be normal or elevated, showing a state of functional iron deficiency. CRP levels are often increased if this is not necessarily the rule (especially when a low-sensitive method of measurement is used). A decrease in serum albumin concentration in the absence of an increase in CRP could also be a marker of inflammation. In the absence of fever or clinical signs of acute infection, procalcitonin dosing is of little help.

The underlying mechanisms that cause anemia of chronic disease are complex and not fully understood; some of them are disease specific and possibly occur concurrently. For example, cancer cells may secrete certain substances that damage or destroy immature red blood cells. In some cases, cancer cells or infectious diseases may infiltrate the bone marrow, the soft spongy material found in long bones where blood cells are formed. More, in general, proinflammatory cytokines, such as tumor necrosis factor (TNF), interleukin (IL)-1 and Il-6, and interferon (IFN), are thought to mediate the pathogenetic process. In particular, IL-6 has been found to antagonize the EPO effect on bone marrow proliferation.

However, the extent to which increased cytokine levels and acute-phase response may contribute to resistance to ESA treatment still is not clear. Back in the nineties, a clear relationship between CRP levels and ESA dose was described in HD patients. Moreover, increased levels of CRP have been found to correlate positively with other inflammatory cytokines, such as IL-6. The serum levels of this cytokine are related directly to ESA dose in HD patients. Similar findings have been shown with TNF- α.

Anemia of chronic disease is generally hypoproliferative, following the inhibition of erythropoiesis in the bone marrow and an absolute or relative impairment of EPO production. A slight shortening of normal red blood cell survival is also often observed.

Many different underlying disorders can cause a state of chronic inflammation, including chronic illnesses such as cancer, certain infections, and autoimmune and inflammatory diseases such as rheumatoid arthritis or lupus. Occult foci of infections or inflammation are also possible; some of them dialysis or CKD specific. The latter include clotted or infected synthetic grafts as vascular access, infection of the central vein catheter, chronic rejection of the renal allograft, periodontal disease, or CKD per se. Indeed, persistent, low-grade inflammation is now considered a hallmark feature of CKD. Recently, gut microbiota dysbiosis, an underestimated source of microinflammation, has been added to the list of possible causes.

The investigation for an underlying reversible cause is mandatory in any patient developing ESA resistance. Treatment of infective causes is obvious when identifiable, together with that of any reversible cause.

Inadequate Dialysis and Online Treatments

In CKD patients, accumulation of uremic toxins is another cause of ESA resistance, possibly interacting at several levels of erythrocyte formation and life. Various polyamines, such as spermine, spermidine, putrescine, and cadaverine, are general bone marrow toxins and thus also suppress erythropoiesis. Others, such as polymeric polyamine–protein conjugates, have been shown to selectively inhibit the erythroid colony-forming units.

Uremic toxins can also inhibit EPO synthesis. Quinolinic acid, which is the product of tryptophan oxidation that increases after enzymatic changes in the kynurenine pathway, accumulates in the presence of renal failure; this substance has a dose-dependent inhibitory effect on EPO gene expression. This action is likely mediated by the hypoxia-inducible factor (HIF) 1 α.

Finally, some protein-bound molecules such as indoxyl sulphate could increase suicidal erythrocyte death, the so-called eryptosis. It is thought that this substance stimulates the entry of extracellular Ca++ with subsequent stimulation of cell shrinkage and expression of phosphotidyl serine on the cell membrane surface, which provides the phagocytic signal. Indoxyl sulphate could also have a pathologic role in inappropriate EPO production by suppressing the transcriptional activity of HIF-1 α. More recently, indoxyl glucuronide, which is another protein-bound uremic toxin, has been shown to inhibit the transcriptional activation of the HIF system at concentrations similar to the blood levels in CKD patients.

In agreement with these experimental observations, a clear relationship among Hb levels, ESA dose, and increase in dialysis dose has been pointed out by a number of prospective or retrospective studies. This is particularly true in patients receiving inadequate dialysis. In recent times, modern dialysis and dialysis filters have a higher depurative capability. As such, only a minority of the patients are truly underdialyzed. However, dialysis dose should be taken into consideration in patients with malfunctioning central vein catheters or fistula, who perform dialysis at low blood flow rates.

Low-level bacterial and endotoxin contamination of water used to generate dialysate may be a cause of chronic inflammation in HD patients, possibly contributing to ESA resistance. Indeed, several studies showed possible benefits on anemia and ESA dose needs when using ultrapure dialysate. Nowadays, thanks to a more widespread use of reverse osmosis systems for the treatment of water, the quality of dialysis water has much improved.

Low-compatible treatments may increase cytokine production and consequently inhibit erythropoiesis. Today, this possibility has become rare, thanks to the availability of good-quality dialysis membranes at reasonable prices.

Starting from the concept that some of the uremic toxins are middle or large molecules, it has been hypothesized that high-flux and online treatments could improve anemia and response to ESAs, following the removal of a higher quantity and types of uremic toxin inhibiting erythropoiesis through an increase in convection. In addition, online treatments give a higher dialysis dose and reduce microbiologic and pyrogenic contamination of the dialysate.

Several small, uncontrolled studies confirmed this hypothesis. However, data from large, randomized clinical studies did not show a significant effect with respect to anemia and ESA needs. It is still controversial whether higher convective volume may have an advantage in this respect. Moreover, when using online treatments, it remains difficult to discriminate between the effect of online hemodiafiltration (HDF) per se and that of an increased dialysis dose. Online HDF may be performed with different substitution modalities. Currently, postdilution HDF is considered the most efficient modality. However, in patients with high predialysis hematocrit levels (covered in this chapter) or low vascular access blood flow, hemoconcentration, coupled with increased shear stress and high pressure inside the dialyzer capillaries, could cause red cell damage and hemolysis. Recently, it has been shown that the use of mixed HDF may allow lower ESA dose needs in comparison to postdilutional HDF. This is possibly due to the fact that with this substitution modality, the predilution and postdilution substitution rates are adjusted by means of a feedback control system to obtain the maximal filtration fraction within safe pressure and hydraulic conditions, thus, preventing progressive hemoconcentration. However, these exploratory findings need further confirmation.

Dialysis adequacy could have an effect on anemia not only in terms of dialysis dose but also in terms of dialysis frequency. Small-scale observations suggest that a more frequent schedule, short daily (for 2 hours 6 times/week) or long nocturnal HD, could enable better control of anemia and a reduction in ESA dose. However, these positive findings are invariably accompanied by an increase in dialysis dose, making it impossible to discriminate a possible role of dialysis frequency per se. These patients also experience lower interdialytic gains in body weight and a lower hemodilution; this may partially account for the observed improvement of anemia. Usually, these are highly selected patients with a low comorbidity burden. Thus, the possible efficacy of daily or nocturnal HD on anemia is not necessarily applicable to patients who are hyporesponsive to ESA therapy.

Malnutrition

Malnutrition is a frequent condition in HD patients, which is directly related to increased morbidity and mortality. Several factors contribute to the progressive development of malnutrition during the course of CKD. This may be a consequence of many factors, including disturbances in protein and energy metabolism, metabolic acidosis, endocrine abnormalities, cardiac failure, infections, and other superimposed illnesses. Reduced food intake because of the anorexia, nausea, and vomiting caused by uremic toxicity (underdialysis) also plays an important role. Moreover, dialytic procedures may enhance protein catabolism as a result of dialytic losses of proteins and amino acids and an inflammatory response to blood–dialyzer interaction.

HD patients tend to reduce food rather than water and sodium intake; for this reason, they often have large interdialytic weight increases contributing to hemodilution and false anemia.

In patients with signs of malnutrition, inadequate vitamin intake should also be taken into account as a possible case of ESA hyporesponsiveness.

For many years, the strict interlink between protein-energy wasting and inflammation has been described in HD patients. Patients with these characteristics often develop severe cachexia; the relative contribution of the single factor is often difficult to be identified. It has been shown that the malnutrition–inflammation complex is an incremental predictor of poor responsiveness to ESAs.

Aluminum Intoxication

Aluminum intoxication is a rare cause of iron-restricted erythropoiesis that may manifest as microcytic hypochromic anemia and, in rare cases, with adynamic bone disease and dementia. In recent years, it has virtually vanished, following restrictions on previous massive use of phosphate binders containing aluminum. Thus, the diagnosis is rarely advocated at present. However, aluminum intoxication can still rarely be observed as a consequence of a defect in dialysis water treatment or excessive content in tap water. In case of proven aluminum intoxication, long-term desferrioxamine infusions during the HD session are recommended, using a stepwise dose increase to prevent an acute decompensation with irreversible neurological lesions.

Pure Red Cell Aplasia

Pure red cell aplasia (PRCA) is a rare condition, defined as severe anemia secondary to the virtual absence of red blood cell precursors in the bone marrow. In CKD patients, PRCA is caused by epoetin-induced antibodies that neutralize all the exogenous ESAs and cross-react with endogenous EPO. Anti-EPO antibodies are polyclonal and neutralize very high concentrations of the native protein. As a result, serum EPO levels are undetectable, and erythropoiesis becomes ineffective.

Clinically, the disease manifests itself as a sudden onset of severe normocytic, normochromic anemia, which is resistant to ESA treatment. Given the almost complete interruption of erythropoiesis, the Hb drop is fast, at a rate corresponding to a red cell life span (nearly 0.1 g/dL/day, slightly less than 1 g/dL/week). Reticulocytes are undetectable ($<10{,}000/mm^3$). The amounts of white blood cells and platelet remain normal.

The diagnosis of ESA-related PRCA needs the exclusion of other PRCA causes, such as thymoma, hematologic conditions (myelodysplasia, B- and T-cell chronic lymphatic leukemia, and chronic myeloid leukemia), autoimmune hemolytic anemia, systemic lupus erythematosus, rheumatoid arthritis, and viral infections (in particular parvovirus B19 and hepatitis B virus). In addition, several drugs can cause PRCA, such as anticonvulsants, antibiotics, and antithyroid agents. The median age at diagnosis is 61 years, with a slight predominance of males. Usually, no correlation is found with the cause of kidney failure. The median duration of ESA treatment before diagnosis is around 7 months, ranging from 1 month to 5 years. Virtually all the reported PRCA cases occurred following the subcutaneous administration of ESAs.

In the early 2000s, a peak increase in the incidence rate of PRCA was observed after a change in the formulation of epoetin alpha produced outside the United States (Eprex). It was hypothesized that a change in the formulation (the substation of human serum albumin with polysorbate 80 as a stabilizer) may have elicited the formation of epoetin-containing micelles that could be immunogenic. Alternatively, leachates released by uncoated rubber stoppers of prefilled syringes may have interacted with polysorbate 80 and acted as an adjuvant of the immune reaction.

The reinforcement of the cold storage chain, the shift toward the IV administration route, and the elimination of uncoated rubber stoppers resulted in the control of the upsurge.

Some years later, the subcutaneous administration of Eprex was again permitted without any new increase in PRCA cases.

Today, PRCA is still rarely observed. In this regard, copies of epoetin alfa produced in low-income countries have a high immunogenic potential caused by suboptimal manufacturing processes. PRCA cases have been described with biosimilars of epoetin alfa approved by the Europe Medicines Agency (EMA). Some years ago, one randomized clinical trial using HX575 was halted for safety reasons following one PRCA case and one anti-EPO antibody positivity. The potential cause of immunogenicity was identified in soluble tungsten, most likely derived from the pins used to manufacture the syringes, causing unfolding and aggregation of HX575 in prefilled syringes. One PRCA case was also described following the use of epoetin zeta.

Given the severe anemia, blood transfusions are often required to maintain acceptable Hb levels. Several immunosuppressant agents have been used to treat PRCA with various rates of success. These include cyclophosphamide, cyclosporine, azathioprine with or without corticosteroids, and antithymocyte globulin. In some cases, rituximab may be effective. Renal transplantation is often resolutive.

After obtaining the complete clearance of anti-EPO antibodies, IV ESA therapy can be cautiously restarted with close monitoring of Hb levels and anti-EPO titers.

Potential Therapeutic Approaches

Despite adequate iron supplementation and ESA use, there are still patients who are unable to reach the desired Hb target range. Thus, we should chart new territories for overcoming ESA hyporesponsiveness. Over the years, many therapeutic strategies have been tried, also in consideration of the high economic impact of this condition; unfortunately, many of them have little clinical effect. In recent years, new agents have been under development to possibly improve anemia management in this troublesome patient population.

Pentoxifylline

Pentoxifylline is a methylxanthine derivative that has been used for many years in the treatment of peripheral vascular

disease for its potent hemorheological properties. The drug also has anti-inflammatory properties since it inhibits monocyte production of TNF-α and T-cell production of both TNF-α and IFN-γ. This ancillary effect has been used in a number of conditions, including idiopathic dilated cardiomyopathy, type 1 diabetes, systemic vasculitis, and rheumatoid arthritis. Oral pentoxifylline has also been tested in HD patients with ESA hyporesponsiveness. One small, open-label study showed remarkable improvement of Hb levels; this went together with significant reduction in the expression of TNF-α and TNF-γ, but no changes were observed in CRP levels. The Handling Erythropoietin Resistance with Oxpentifylline (HERO) Trial was a randomized, placebo-controlled study testing the efficacy of pentoxifylline in 53 patients with CKD stage 4 or 5 (including dialysis) and ESA-hyporesponsive anemia. Pentoxifylline significantly increased Hb levels in comparison to the placebo, but without a significant difference on ERI. Of note, the study had a much smaller sample size than the planned one due to slow recruitment. Similarly, a meta-analysis of 11 studies (377 patients) including seven randomized controlled trials did not show conclusive effects of pentoxifylline on anemia, ESA dose, and iron parameters.

At present, there is not enough evidence supporting the utility of pentoxifylline for improving anemia control in HD patients in clinical practice.

L-Carnitine

L-Carnitine is important for fatty acid metabolism; patients on dialysis are often in a chronic carnitine-deficient state, partially because of its removal with dialysis. The condition may be associated with abnormalities in fatty acid and organic acid metabolism. Years ago, it was hypothesized that L-carnitine could improve red cell survival. Observations have linked high ERI with subnormal L-carnitine levels (< 30 μM) and the ratio of non–acetyl acylcarnitines/total carnitine. As shown by a meta-analysis, at present, there is no evidence that L-carnitine supplementation can improve anemia, inflammation, and oxidative stress in HD patients. However, available studies have several methodological limitations.

Ascorbic Acid

Ascorbic acid is a powerful enhancer of non-heme iron absorption; it can also improve iron release from body stores, making it available for erythropoiesis. Some studies showed some improvement of Hb levels together with a decrease in ESA doses following the IV administration of ascorbic acid. However, to obtain the effect, high doses are required, which can be associated with important side effects, including the severe risk of oxalosis.

AST-120

AST-120 is an inert binding compound; it is able to reduce indoxyl sulfate (IS) plasma levels and has antioxidant activity. It has been proposed as a possible therapeutic strategy for improving ESA response. Some years ago, Wu et al. performed a crossover study of 50 predialysis CKD patients and showed some benefit of AST-120 in respect of anemia. In addition, the drug significantly reduced IS and *p*-cresyl sulfate (PCS) levels.

Androgens

Before ESA availability, androgens were largely used to improve anemia in HD patients. However, their efficacy was poor, and they had many side effects. Their use is no longer recommended.

Vitamin D

Several observational studies demonstrated that lower 25(OH) D_3 and higher CRP levels are independently associated with lower Hb concentrations. Treatment with cholecalciferol of 158 HD patients resulted in a reduction of CRP and ESA dose, suggesting a possible effect of vitamin D analog in preventing anemia related to inflammation and ESA hyporesponsiveness. These effects are not related to parathyroid hormone (PTH) values and seem to be independent of PTH suppression. A possible explanation may be that calcitriol directly stimulates erythroid progenitors. As an alternative, vitamin D could behave as a modulator of innate and adaptive immunity.

Antioxidant and Vitamin E–Coated Dialyzers

Oxidative stress is commonly observed in HD patients; it is the result of an imbalance between overproduction of reactive oxygen species and impairment of defense mechanisms. The dialysis procedure further exposes HD patients' oxidative stress through the contact with the dialysis membrane and dialysate; the loss of low molecular weight antioxidants may also have a contributory role. Given that oxidative stress has an interlink with proinflammatory cytokine and uremic toxins, it may also influence the severity of anemia and ESA response.

Accordingly, 8-hydroxy-2'-deoxyguanosine, which is a product of oxidized DNA, was found associated with ESA resistance in HD patients. Unfortunately, as a whole, trials on antioxidant vitamins had disappointing results in HD patients. The use of vitamin E–coated dialyzers has also been proposed to prevent the oxidative stress linked to the bioincompatibility of the dialysis procedure. Some years ago, a randomized, crossover pilot study suggested a possible positive effect of the polysulfone vitamin E–coated dialyzer on ESA response, particularly in patients with a higher ERI at baseline. However, a multicenter randomized controlled trial showed some efficacy when adjusting the analysis for baseline ERI values. At the multivariate analysis, treatment group and baseline ERI with their interaction explained 15% of the total variability of ERI changes during follow-up.

Other clinical studies evaluated the effects of vitamin E–coated dialyzers with respect to oxidative stress, inflammation, and ESA requirements, with conflicting results.

Altogether, data from the literature seem to suggest that the higher ERI at baseline is, the higher is the positive effect of the vitamin E–coated dialyzers.

Prolyl-Hydroxylase Domain Inhibitors

Prolyl-hydroxylase domain (PHD) inhibitors are oral agents that stimulate the production of endogenous EPO and effectively correct and maintain Hb levels in CKD patients. These molecules have received marketing authorization in China, Japan, and Chile and are either in an advanced phase of clinical development or are undergoing evaluation for approval by the Food and Drug Administration (FDA) and European Medicine Agency (EMA).

PHD is a family of enzymes that regulates the expression of the HIFα in response to either hypoxia or iron availability. Under hypoxia or pharmacological inhibition, PHD activity decreases, and HIFα can then bind to the HIFβ subunit, translocate into the nucleus, and control broadly the physiological response to hypoxia, including the stimulation of erythropoiesis and the absorption and mobilization of iron.

Accordingly, PHD inhibitors significantly decrease hepcidin levels (mainly indirectly) and directly enhance the effect of other regulators of iron transport, with a final effect of improved iron availability. Moreover, the HIF system has a role in some inflammatory processes. Data from phase II studies showed that dose needs with roxadustat were unrelated to CRP values. More robust findings have been shown by preliminary communications of the findings of phase III trials. A pilot study tested the efficacy of daprodustat in 15 hyporesponsive patients. At week 16, half of the patients had suboptimal efficacy, partially because of insufficient compliance in some patients and by choice of a too low starting dose. Interestingly, high-sensitive CRP decreased during the study. Overall, these agents have the potential to become a new therapeutic strategy for patients who are hyporesponsive to ESAs.

Antihepcidin Drugs

Patients who are hyporesponsive to ESAs often have functional iron deficiency due to the entrapping effect of serum hepcidin on iron stores, limiting iron availability for erythropoiesis. For this reason, hepcidin is considered a possible therapeutic target in general for anemia of chronic disease. Lexaptepid pegol, which is an antihepcidin spiegelmer, has been developed. However, it is still at an early phase of clinical development. Hepcidin suppression can also be obtained by regulating some of its regulatory pathways, such as bone morphogenetic protein 6 (BMP6) and intranuclear SMAD4. Recently, a fully human anti-BMP6 antibody has been shown to reduce the need for EPO in rodent models of the anemia of chronic disease. As an alternative, other compounds under development capture serum hepcidin to prevent ferroportin degradation.

Conclusions

In summary, improving the outcomes of ESA-resistant patients require complete patient assessment that goes beyond considerations of iron and ESA dose alone. Given that ESA dose is associated with mortality, mitigating ESA resistance may improve patient outcomes.

Owing to the multifactorial pathogenesis of ESA hyporesponsiveness, new potential strategies for the management of ESA hyporesponsiveness are regarded with particular interest. The ongoing trials on novel therapeutic approaches for correcting anemia of CKD patients, including hepcidin modulation, EPO gene therapy, and HIF stabilization, are awaited with much interest, especially in ESA hyporesponsive patients.

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39

Chronic Kidney Disease–Mineral and Bone Disorder

WEI CHEN, MD • DAVID BUSHINSKY, MD

Introduction

Patients with CKD often have disturbances in divalent ion metabolism, including the dysregulation of calcium and phosphorus, bone disease, and extraosseous calcification. These disturbances were previously referred to as renal osteodystrophy. However, the term *renal osteodystrophy* is primarily a description of altered bone morphology in patients with CKD. In 2006, the Kidney Disease: Improving Global Outcomes (KDIGO) proposed a new term called CKD-MBD. CKD-MBD is defined as a systemic disorder of mineral and bone metabolism due to CKD and is manifested by either one or a combination of the following: (1) abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism; (2) abnormalities in bone turnover, mineralization, volume, linear growth, or strength; and (3) vascular or other soft-tissue calcification.

Pathophysiology of Chronic Kidney Disease–Mineral Bone Disorder

Chronic kidney disease (CKD)–mineral bone disorder (MBD) is a complex disorder that involves physiologic feedback loops among kidneys, intestine, bone, and vasculature. It is characterized by phosphate retention and secondary hyperparathyroidism. Before discussing the pathophysiology of secondary hyperparathyroidism, we briefly review the regulation and action of the hormones that are involved in mineral metabolism: parathyroid hormone (PTH), vitamin D, and fibroblast growth factor-23 (FGF23).

Review of Parathyroid Hormone, Vitamin D, and Fibroblast Growth Factor-23

PTH is secreted by the chief cells of the parathyroid glands. PTH level increases primarily in response to a fall in arterial blood ionized calcium but also in response to a fall in calcitriol (1,25-dihydroxyvitamin D, the activated form of vitamin D) and an increase in serum phosphate level. PTH increases the concentration of calcium by increasing bone resorption, enhancing calcium reabsorption from the thick ascending limb and distal renal tubule in the kidneys, and increasing the production of calcitriol, which leads to an increase in intestinal calcium absorption. PTH reduces renal reabsorption of phosphate in the proximal tubule, thus lowering serum phosphorus. However, by inducing bone resorption and increasing calcitriol-mediated intestinal phosphate absorption, PTH also raises the level of serum phosphorus.

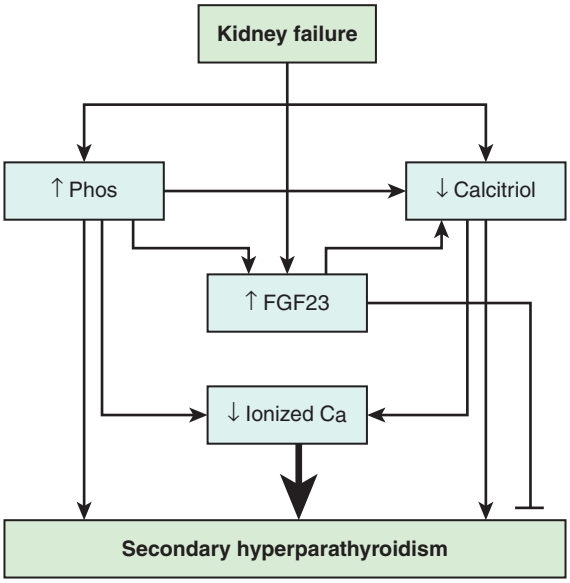
Cholecalciferol (vitamin D_3) is a fat-soluble steroid that is synthesized in the skin in the presence of ultraviolet light or obtained from the diet. In the liver, it is converted to 25-hydroxyvitamin D by 25-hydroxylase. 25-Hydroxyvitamin D then enters the circulation and is hydroxylated in the proximal tubules of kidneys to calcitriol (1,25-dihydroxyvitamin D), which is the most biologically active form of vitamin D. Calcitriol production is increased by PTH, a low arterial concentration of both calcium and phosphorus. Calcitriol increases intestinal absorption of calcium and phosphate and, at high levels, induces bone resorption and perhaps renal tubular calcium reabsorption. Calcitriol also lowers PTH levels, limiting urinary phosphate excretion.

FGF23 is a hormone produced in osteocytes and osteoblasts. Its primary stimulus remains unclear but appears to involve phosphorus retention. In kidneys, FGF23 binds to the klotho-FGF receptor complex and induces phosphaturia by down-regulating sodium-phosphate cotransporter in the proximal tubule. FGF23 also inhibits PTH secretion by binding to receptors on the parathyroid glands and decreases calcitriol production, which decreases intestinal phosphorus absorption. Elevated levels of FGF23 are associated with kidney disease progression, left ventricular hypertrophy, endothelial dysfunction, vascular stiffness, and high mortality rate in patients with CKD.

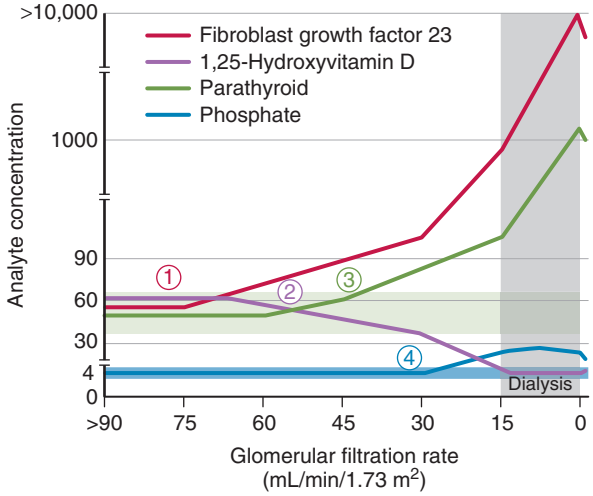
Development of Secondary Hyperparathyroidism in Chronic Kidney Disease

Phosphate excretion decreases as renal function declines. With a constant dietary intake of phosphorus and the majority of phosphorus being absorbed, phosphate is retained. Phosphate retention reduces ionized calcium by directly binding with calcium, as well as stimulating FGF23 release from osteocytes and decreasing calcitriol synthesis. The reduced level of ionized calcium leads to an increase in PTH. The decreased calcitriol concentration in CKD appears to be secondary to a combination of an increase in FGF23 concentration, loss of functional renal mass, and phosphate retention. The pathophysiology of secondary hyperparathyroidism in patients with CKD is illustrated in Fig. 39.1.

If elevated PTH is a normal physiologic response to low ionized calcium, why is secondary hyperparathyroidism a disorder? In the 1970s, Bricker and Slatopolsky proposed the "trade-off" hypothesis for the development of secondary hyperparathyroidism. The idea of the "trade-off" hypothesis is that the body pays a biological "price" (i.e., PTH excess) in order to maintain normal levels of calcium and phosphorus. At some increased levels of PTH, this response appears to be maladaptive because although PTH is phosphaturic, it increases serum phosphorus by increasing bone resorption.



• **Fig. 39.1** Pathophysiology of Secondary Hyperparathyroidism. When renal failure occurs, phosphate retention develops. Phosphate retention ultimately leads to decreased ionized calcium, which promotes parathyroid hormone (PTH) release and development of secondary hyperparathyroidism. Phosphate retention reduces ionized calcium by directly binding with calcium, as well as by stimulating FGF23 release from osteocytes and decreasing calcitriol synthesis. The decreased calcitriol concentration in chronic kidney disease is secondary to the combination of loss of renal function, increase in FGF23 concentration, and phosphate retention. Phosphate retention can also directly stimulate PTH gene expression and increase PTH synthesis independent of the ionized calcium concentration and calcitriol level. Contrarily, elevated FGF23 levels may inhibit the secretion of PTH. *FGF23*, Fibroblast growth factor-23.



• **Fig. 39.2** Temporal Sequence of Disordered Phosphorus Metabolism in Progressive Chronic Kidney Disease (CKD). The y-axis represents circulating concentrations of the individual analytes with the temporal changes. The individual analytes are color-coded (C-terminal FGF23 [RU/mL] in *red*; 1,25-dihydroxyvitamin D [pg/mL] in *purple;* parathyroid hormone [PTH] [pg/mL] in *green*; and phosphate [mg/dL] in *blue*). Current hypotheses propose increased FGF23 as the earliest alteration in mineral metabolism in CKD (no. 1, *red*). Gradually increasing FGF23 levels cause the early decline in $1,25(OH)_2D$ levels (no. 2, *purple*) that free PTH from feedback inhibition, leading to secondary hyperparathyroidism (no. 3, *green*). All of these changes occur long before increase in serum phosphate levels is evident (no. 4, *blue*). (Adapted from Wolf M. Forging forward with 10 burning questions on FGF23 in kidney disease. *J Am Soc Nephrol*. 2010;21:1427–1435.)

As renal function deteriorates, the effect of PTH on urinary phosphate excretion diminishes, and the excess PTH exacerbates hyperphosphatemia by increasing bone resorption and leading to significant bone disease.

The temporal sequence of disordered phosphorus metabolism in progressive CKD is demonstrated in Fig. 39.2. The prevalence of hyperphosphatemia is elevated FGF23, and PTH levels increase progressively with worsening kidney function. Alterations in FGF23, PTH, and calcitriol are physiologic responses to prevent the increase in serum phosphorus. An increase in FGF23 is detected first, well before the development of CKD stage 3. Elevated FGF23 levels lead to a decreased production of calcitriol and, subsequently, development of secondary hyperparathyroidism. The serum level of phosphorus begins to increase when the estimated glomerular filtrate rate (eGFR) falls below approximately 60 mL/min/1.73 m^2 but remains in a relatively normal range until eGFR is less than approximately 30 mL/min/1.73 m^2. Serum phosphate, FGF23, and PTH levels continue to rise as renal function declines.

Disordered Mineral Metabolism and Mortality

Increased FGF23 levels appear to be independently associated with mortality in patients with advanced CKD. In a study with patients who were beginning hemodialysis

treatment, increasing FGF23 levels were associated with a monotonically increased risk of death in a year and compared to hemodialysis patients with FGF23 levels in the first quartile, the odds of dying were 4 to 5 times higher for those with FGF23 in the third or fourth quartile.

The relationships of serum calcium, phosphorus, and PTH with mortality are U shaped, with very low and very high levels associated with increased mortality. According to the data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) 1996–2007, the lowest mortality risk was observed with serum calcium between 8.6 and 10.0 mg/dL (albumin-corrected calcium between 7.6 and 9.5 mg/dL), phosphorus between 3.6 and 5.0 mg/dL, and PTH between 101 and 300 pg/mL. Mortality was the highest when serum calcium was >10.0 mg/dL, phosphorus >7.0 mg/dL, and PTH >600 pg/mL.

In the dialysis population, both hypocalcemia and hypercalcemia are associated with high all-cause mortality, and hypercalcemia is closely associated with cardiovascular mortality. The prevalence of hypocalcemia, defined as serum calcium <8.5 mg/dL, is ~11% in patients on dialysis. Patients on dialysis develop hypocalcemia due to phosphate retention and reduced levels of calcitriol. The prevalence of hypercalcemia, defined as serum calcium >10.2 mg/dL, is slightly lower at ~5%. The causes of hypercalcemia in patients on dialysis include the use of calcium-containing phosphate binders, vitamin D analogs, high dialysate calcium concentration, and development of tertiary hyperparathyroidism.

Hyperphosphatemia is a late manifestation of CKD with a prevalence of more than 50% when eGFR is <20 mL/min/1.73 m^2. In an observational cohort using the data of prevalent and incident patients on maintenance dialysis (both hemodialysis and peritoneal dialysis [PD]), participants with serum phosphorus ≥6.4 mg/dL had an increased risk of all-cause and cause-specific mortality: comparing participants with serum phosphorous level ≥6.4 mg/dL with those with normal serum phosphorous level (i.e., 4.5 to <5.4 mg/dL), the adjusted hazard ratio of all-cause mortality was 1.50 (95% confidence interval [CI], 1.47–1.54) for patients on hemodialysis and 1.48 (95% CI, 1.34–1.63) for patients on PD.

Similarly, both hypoparathyroidism and hyperparathyroidism in patients on dialysis are associated with higher mortality. According to the DOPPS data, compared to PTH between 101 to 300 pg/mL, PTH ≤100 pg/mL was associated with significantly greater cardiovascular mortality, and PTH >600 pg/mL was associated with both higher all-cause and cardiovascular mortality.

Bone Disease

Bone Disease in Chronic Kidney Disease

In 2006, Kidney Disease: Improving Global Outcomes (KDIGO) recommended a new system to describe bone pathology in patients with CKD. This system describes three key histologic features observed in the bone of patients with CKD: turnover, mineralization, and volume. There are four major types of bone diseases that occur in patients with CKD: adynamic bone disease, osteitis fibrosa cystica, osteomalacia, and mixed uremic osteodystrophy (Table 39.1). Adynamic bone disease is characterized by low bone turnover, which is often the result of excessive PTH suppression. Osteitis fibrosa cystica is characterized by high bone turnover and is due to secondary hyperparathyroidism. In the past decades, with the development of better phosphorus binders and the use of cinacalcet and vitamin D analogs, the prevalence of osteitis fibrosa cystica has markedly decreased, while the prevalence of adynamic bone disease has increased. Osteomalacia is characterized by low bone turnover and abnormal mineralization. It was once primarily due to aluminum deposition in bone when aluminum-containing phosphate binders were utilized and when aluminum was present in water used for dialysis. Osteomalacia is uncommon now after the discontinuation of high-dose aluminum-containing phosphate binders and incorporation of reverse osmosis devices in dialysis water treatment systems. Mixed uremic osteodystrophy is characterized by either high or low bone turnover as well as abnormal mineralization. The symptoms of bone disease usually only occur in severe cases and may include bone tenderness, fracture, muscle weakness, and arthritis. Both high- and low-turnover bone diseases are associated with increased fracture risk.

Patients with Chronic Kidney Disease Have More Hip Fractures

Patients with CKD have more hip fractures compared to patients without kidney disease. According to the Third National Health and Nutrition Examination Survey (NHANES),

TABLE 39.1 Major Types of Bone Diseases in Chronic Kidney Disease

	Turnover	Mineralization	Volume	Etiology
Adynamic bone disease	Low	Abnormal	Low	Excessive suppression of parathyroid glands
Osteitis fibrosa cystica	High	Abnormal	Increased	Secondary hyperparathyroidism
Osteomalacia	Low	Abnormal	Abnormal	Aluminum deposit
Mixed uremic osteodystrophy	High or low	Abnormal	Abnormal	—

compared to those with eGFR > 100 mL/min/1.73 m^2, participants with eGFR < 60 mL/min/1.73 m^2 have a twofold increase in the likelihood of reporting a previous hip fracture. A recent meta-analysis showed that patients with CKD stage 3 to 5D had a significant increase in fracture risk both for hip (relative risk, 2.36; 95% CI, 1.64–3.39) and nonvertebral fracture (relative risk, 1.47; 95% CI, 1.15–1.88), and the risk of fracture increased with worsening kidney function. According to the U.S. Renal Data System (USRDS), between 1989 and 1996, the overall incidence of hip fracture was 7.45 per 1000 person years for males and 13.63 per 1000 person years for females with end-stage kidney disease (ESKD). The overall relative risk for hip fracture was ~4.4 for dialysis patients compared with people of the same sex in the general population. Patients on hemodialysis have a higher risk of hip fractures compared to patients on PD. In both the general and the dialysis population, hip fracture is associated with high mortality.

Diagnosing Bone Disease

Bone biopsy with histomorphometric analysis is the gold standard for diagnosing bone disease in patients with CKD and can be very helpful in determining the clinical course and response to treatment. KDIGO recommends that in patients on chronic dialysis, it is reasonable to perform a bone biopsy in various settings, including, but not limited to, unexplained fractures, persistent bone pain, unexplained hypercalcemia, or hypophosphatemia, possible aluminum toxicity, and prior to initiation of bisphosphonate therapy. This recommendation is not graded, and there remains controversy over the indications for bone biopsy. Overall, bone biopsies are not routinely performed clinically, and there are several reasons for this. Since aluminum toxicity is now rare and both high- and low-turnover bone disease are associated with increased fracture risk, there are few circumstances (perhaps in the case of determining if bisphosphonate therapy is appropriate) in which the precise knowledge of bone pathology will change management. In addition, few nephrologists are trained to perform bone biopsies, and few pathologists have expertise in reading the biopsies.

Besides bone biopsy, there is no other method to adequately determine the underlying bone histology in patients with CKD. Although circulating intact PTH levels may indicate the presence and severity of hyperparathyroidism, they are not strong predictors of the underlying bone disease or useful in defining the type of renal osteodystrophy. Some biochemical markers of bone resorption, such as serum C-telopeptide of type I collagen, have been studied to help diagnose bone disease in CKD, but none has been shown to be clinically useful.

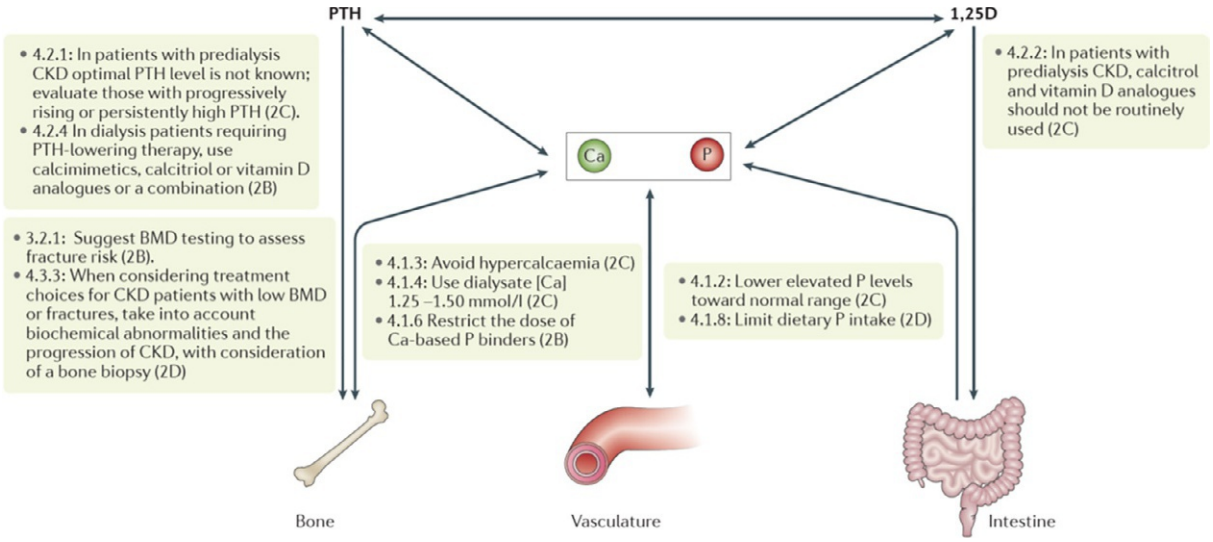
In the general population, dual-energy x-ray absorptiometry (DXA) is the clinical standard to screen and stratify fracture risk. In patients with CKD, fracture risk screening by DXA has been controversial. Due to the lack of supporting evidence, the 2009 KDIGO guidelines recommended that bone mineral density testing not be performed routinely in CKD patients. However, since then, several studies have found that bone mineral density measured by DXA predicted fractures across the spectrum from CKD stage 3a to 5D. In a study of 485 hemodialysis patients in Japan, bone mineral density at every site, except whole body or lumbar spine, had significant power to discriminate prevalent spine fracture, and in women, with PTH < 204 pg/mL, bone mineral density at the hips was predictive of any incident fracture. In recognition of the new information, in 2017, KDIGO updated their recommendations on CKD-MBD and suggested bone mineral density testing to assess fracture risk if results will impact treatment decisions (level 2 recommendation: Fig. 39.3). However, it is important to recognize that bone mineral density does not discriminate high versus low turnover bone disease, which is important to clinical management.

High-resolution peripheral quantitative computed tomography (HR-pQCT) is a novel imaging tool. It is a noninvasive, low-radiation method to assess three-dimensional bone microarchitecture and volumetric bone mineral density in cortical and trabecular compartments of the distal radius and distal tibia. Since its availability in the mid-2000s, its application in clinical research has increased significantly. However, its utility in clinical practice for fracture prediction remains unclear.

Vascular Calcification

Vascular Calcification and Cardiovascular Mortality

Vascular calcification is common in patients with CKD, with a prevalence as high as 80%. Multiple studies have demonstrated that the extent of vascular calcification is a predictor of cardiovascular morbidity and mortality in CKD. Vascular calcification occurs in both the intima and media of vessel walls. Intimal calcification is an indicator of atherosclerosis. In coronary arteries, it is positively correlated with atherosclerotic plaque burden and contributes to ischemic heart disease. Medial calcification is a characteristic feature of CKD and diabetes mellitus and is closely associated with dialysis duration and disordered mineral metabolism. The unique feature of medial calcification in CKD is supported by both the presence of vascular calcification in young CKD patients, who had no traditional risk factors for atherosclerosis, and a high prevalence of medial calcification in the epigastric arteries of patients with ESKD at the time of kidney transplantation. Medial calcification causes arterial stiffness and decreases vessel compliance. This loss of shock-absorbing function of arteries may lead to systolic hypertension and increased afterload, resulting in left ventricular hypertrophy and subsequent heart failure. Increased afterload also compromises coronary perfusion and exacerbates ischemic heart disease. Medial calcification also appears to be responsible for calcific uremic arteriopathy



• **Fig. 39.3** Revised Recommendations From the 2017 KDIGO Update on CKD-MBD. Only recommendations that are graded and apply to patients with chronic kidney disease and no history of kidney transplantation are shown, alongside the chapter from which the recommendation appears. Nomenclature for grading recommendations is as follows: level 2 (2, "we suggest") indicates that different choices will be appropriate for different patients; grade B (B) indicates moderate quality evidence; C, low-quality evidence; D, very low-quality evidence. *1,25D*, 1,25-dihydroxyvitamin D; *BMD*, bone mineral density; *Ca*, calcium; *[Ca]*, calcium concentration; *CKD*, chronic kidney disease; *MBD*, mineral and bone disorder; *P*, phosphorous; *PTH*, parathyroid hormone. (Adapted from Chen W, Bushinsky DA. Chronic kidney disease: KDIGO CKD-MBD guideline update: evolution in the face of uncertainty. *Nat Rev Nephrol*. 2017;13(10):600–602.)

or calciphylaxis, which is a systemic calcification of arterioles leading to ischemia and subcutaneous necrosis.

Risk Factors for Vascular Calcification

Vascular calcification is not only a passive process but also an active regulated cell-mediated process. There are several risk factors that predispose patients with CKD to vascular calcification. The traditional risk factors include older age, diabetes mellitus, dyslipidemia, and inflammation. There are also risk factors that are more specific to CKD, including disordered mineral metabolism, therapies used to treat secondary hyperparathyroidism, and used during dialysis treatment. Use of 1,25-dihydroxyvitamin D or its analog in an effort to lower PTH levels, especially in conjunction with calcium-containing phosphorous binders, can lead to increased gastrointestinal absorption of calcium. Elevated serum calcium and phosphorus levels can lead to the phenotypic transition of vascular smooth muscle cells in the arterial media to osteoblast-like cells and enhanced matrix mineralization, leading to vascular calcification. The 2017 KDIGO update on CKD-MBD suggests against the routine use of calcitriol or vitamin D analog in patients with predialysis CKD, and in those receiving phosphate-lowering treatment, the guidelines suggest restricting the dose of calcium-base phosphate binders (Fig. 39.3).

Diagnosing Vascular Calcification

Current guidelines do not recommend routine screening for vascular calcification. Detection of vascular calcification using any technique has not been shown to have any clinical utility in terms of risk stratification or therapy. Electron-beam computed tomography (CT) is thought to be the gold standard to detect and quantify vascular calcification. The magnitude of coronary artery calcification imaged using electron-beam CT is a strong predictor of cardiovascular mortality. Due to the high dose of radiation exposure, the utility of electron-beam CT is generally limited to research. Plain radiography, although not as sensitive as electron-beam CT, can also be used to detect vascular calcification. The National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines suggest using plain radiography as an imaging modality, specifically lateral abdominal radiograph if a practitioner chooses to assess calcification. There are two scoring systems that have been developed to quantify vascular calcification systemically using plain radiography. They are the Kauppila and Adragao scores. Kauppila scores evaluate lumbar aortic calcification. The segments of abdominal aorta in front of the lumbar spine L1–L4 are assessed. Adragao scores assess calcification in muscular arteries, including the iliac, femoral, radial, and digital arteries. Plain radiographs of the hands and pelvis are taken. Both high Kauppila and Adragao scores are associated with high cardiovascular mortality in patients with CKD. Since medial calcification can lead to arterial stiffness, ankle-brachial index and pulse wave velocity can also be used to assess vascular calcification indirectly.

In the past decade, the properties of serum calciprotein particles have been studied as a marker of vascular calcification. Calciprotein particles are nanoparticles that are composed of calcium phosphate crystals and calcification

inhibitors. They are thought to mediate the clearance of excess calcium and phosphate in the circulation. There are two types of calciprotein particles, primary and secondary. Primary calciprotein particles are smaller and soluble, and they are probably the predominant form of circulating calciprotein particles. Secondary calciprotein particles are larger and more crystalline. In vitro, primary calciprotein particles spontaneously transform into secondary calciprotein particles. The half-maximal time of transformation from primary to secondary calciprotein particles is referred to as T_{50}. In patients with predialysis CKD, a low T_{50} or a fast transformation from primary to secondary calciprotein particles has been associated with the severity and progression of coronary artery calcification in those with prevalent coronary artery calcification at baseline. Measuring the transformation of serum calciprotein particles is currently limited to research settings.

Bone-Vascular Axis

Current literature suggests that there is a direct biological interplay between bone and vascular systems. Numerous epidemiologic studies demonstrated an inverse relationship between vascular calcification and bone density (i.e., patients with lower bone mass are more likely to have greater vascular calcification). The relationship is well documented in the general population, postmenopausal women, and dialysis patients, and the association persists after adjusting for age. The mechanism linking bone activity and vascular calcification is complex and not well understood. Vascular calcification is an actively regulated cell-mediated process with promoters and inhibitors of calcification. When exposed to a pathogenic environment, vascular smooth muscle cells undergo phenotypic changes to transition to osteoblast-like cells and lay down collagen, which may then become mineralized and lead to overt vascular calcification. Several mechanisms have been proposed to explain the link between bone development and vascular calcification: (1) there are several common factors that are involved in bone remodeling and calcification, such as osteoprotegerin and activator of the nuclear factor-kappa B ligand system; (2) atherosclerosis of bone vessels may compromise bone blood supply affecting bone integrity; and (3) circulating complexes released from bone turnover, such as calcium/phosphate, may promote vascular calcification. More research to investigate this complex bone-vascular axis is needed.

Treatment

Management of CKD-MBD includes control of phosphorus, calcium, and PTH. It involves optimizing dietary phosphate intake, administration of phosphate binders, use of calcimimetics and vitamin D, and an appropriate dialysis prescription. For patients with severe hyperparathyroidism that is refractory to medical therapies, parathyroidectomy may be necessary. In this section, we discuss treatment targets and dietary phosphate and provide an overview of medical management. Phosphate binders, vitamin D therapy, and parathyroidectomy are discussed in greater detail in subsequent chapters.

Treatment Targets

The NKF-KDOQI guidelines in 2003 suggest the following optimal treatment targets for patients on dialysis: corrected serum calcium between 8.4 and 9.5 mg/dL, serum phosphorus between 3.5 and 5.5 mg/dL, and PTH between 150 and 300 pg/mL. In 2009, KDIGO (an independent international organization) proposed a different clinical practice guideline for the treatment of CKD-MBD. In 2010, NKF published a commentary summarizing the KDOQI and KDIGO guidelines and put the KDIGO guideline into the context of the supporting evidence and the setting of care delivered in the United States. These guidelines are summarized in Table 39.2. It is important to note that current practice guidelines are largely based on observational studies and expert opinion. There are no interventional randomized controlled trials to demonstrate that correcting the abnormalities in mineral metabolism (serum calcium, phosphorus, and PTH) will improve cardiovascular outcomes and patient survival.

TABLE 39.2 Treatment Targets Recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) 2003 and Kidney Disease: Improving Global Outcomes (KDIGO) 2009 for Patients on Dialysis

	KDOQI	KDIGO	KDOQI Commentary*
Serum calcium	8.4–9.5 mg/dL	Maintain in normal reference range	–
Serum phosphorus	3.5–5.5 mg/dL	Lower toward normal range	–
Parathyroid hormone (PTH)	150–300 pg/mL	Maintain within ~2–9 times the upper reference limit	Wide target range: ~130–600 pg/mL

*Uhlig K, Berns JS, Kestenbaum B, et al. KDOQI U.S. commentary on the 2009 KDIGO Clinical Practice Guideline for the diagnosis, evaluation, and treatment of CKD–mineral and bone disorder (CKD-MBD). *Am J Kidney Dis.* 2010;55(5):773–799.

Dietary Phosphate

Phosphorus is ingested from food as a constituent of phosphoprotein, phospholipids, and nucleotide phosphates. The typical Western diet has a high phosphate content, which comes from dairy products and protein sources. The KDOQI guidelines suggest to restrict dietary phosphate to 800 to 1000 mg per day when serum phosphorus levels are > 4.6 mg/dL in CKD stages 3 and 4 and > 5.5 mg/dL in CKD stage 5. Since protein-energy malnutrition is highly prevalent in patients on chronic dialysis, we generally do not recommend dietary protein restriction. Rather, it is important to differentiate the source of protein and phosphate.

In general, animal protein has higher phosphorus bioavailability compared to plant protein. Foods with a high phosphate load include nuts, hard cheeses, egg yolk, meat, poultry, and fish. Plant protein, especially grains, has a lower phosphate-to-protein ratio because most of the phosphate is in the form of phytate, which is not absorbed. Moe et al. conducted a crossover trial of nine patients with a mean eGFR of 32 mL/min/1.73 m^2 to compare the serum phosphorus and other hemostatic response to dietary phosphate intake after ingesting either meat or vegetarian diet of equivalent nutrients. They found that 1 week of a vegetarian diet lowered serum phosphorus and FGF23 levels. This study showed that the source of protein had a significant effect on phosphorous hemostasis in CKD.

In addition to the phosphate load from food, food additives also contribute significantly to phosphate retention in patients with CKD. Phosphorus in the form of phosphate salts (e.g., phosphoric acid, pyrophosphate, polyphosphate, and phosphate) is used in industrial food processing as food preservatives and as a color or flavor enhancer. Inorganic phosphate salts from the additives are almost completely absorbed in the gastrointestinal tract. Phosphorus additives are common, and the amount of phosphorus load is considerable compared to the phosphorus content in natural food. Leon et al. reviewed the food labels of ~2400 best-selling branded grocery products and found that 44% of these grocery items contained phosphorus additive—prepared frozen food (72%), dry food mixes (70%), packaged meat (65%), bread and baked goods (57%), and yogurt (51%). They also sampled meals for 4 days consisting of foods with and without phosphorus additive and found that meals composed mostly of phosphorus additives–containing foods had 736 mg more phosphorus per day compared with meals consisting of phosphorus additive-free foods.

It can be challenging to limit dietary phosphate intake because many foods contain phosphorus; thus, it is crucial to differentiate the source of phosphorus, choose plant protein over animal protein, and avoid foods with phosphorus-containing additives. Boiling can also reduce the phosphorus content in foods. The degree of mineral loss (calcium, phosphorus, sodium, and potassium) is proportional to the cooking time, amount of boiling water, and the size of the pieces.

Medical Management

Medical management of CKD-MBD includes oral phosphate binders, calcimimetics, and activated vitamin D therapy (Table 39.3). Oral phosphate binders limit the absorption of dietary phosphate and include calcium-containing and non-calcium-containing binders. Calcium-containing binders are less costly compared to non-calcium-containing binders, but they may result in a positive calcium balance and vascular calcification, resulting in higher cardiovascular mortality. The impact of calcium load from calcium-containing binders on vascular calcification is greater in the presence of adynamic bone disease. In an open-label randomized, controlled trial of 466 incident hemodialysis patients recruited from 18 centers in Italy, patients treated with sevelamer (which does not contain calcium) had lower cardiovascular and all-cause mortality than those treated with calcium carbonate. A meta-analysis of 4770 participants (88% on hemodialysis) also showed that patients receiving sevelamer had lower all-cause mortality (risk ratio, 0.54; 95% CI, 0.32–0.93) compared with those on calcium-containing binders, but there was no statistically significant difference in cardiovascular mortality.

Aluminum-containing binders are no longer used because of aluminum toxicity, which can manifest as dementia,

TABLE 39.3 Medical Treatment of CKD-MBD

Phosphate Binders
Calcium-Containing Binders
Calcium carbonate
Calcium acetate
Non-Calcium-Containing Binders
Sevelamer hydrochloride/carbonate
Lanthanum carbonate
Sucroferric oxyhydroxide
Ferric citrate
Nicotinamide
Aluminum hydroxide/carbonate
Vitamin D Therapy
Vitamin D Derivative
Calcitriol (1,25-dihydroxycholecalciferol)
Vitamin D Analogs
Doxercalciferol
Paricalcitol
Alfacalcidol
Falecalcitriol
22-Oxacalcitriol
Calcimimetics
Cinacalcet
Etelcalcetide

CKD, Chronic kidney disease; *MBD*, mineral and bone disorder.

osteomalacia, anemia, and arthritis. Iron-based phosphate binders, such as ferric citrate, are relatively new agents. Ferric citrate appears comparable to sevelamer in terms of phosphorus control and supplies iron, which may help to maintain hemoglobin levels.

Calcimimetics increase the sensitivity of the calcium-sensing receptor on the parathyroid glands to calcium and result in a substantial reduction in PTH and also lower calcium, phosphorus, and FGF-23. Because of the hypocalcemic effect of calcimimetics and the risk of symptomatic hypocalcemia, calcimimetics should not be started if serum calcium is < 8.4 mg/dL. The EVOLVE (Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events) trial tested the hypothesis that treatment with cinacalcet might reduce the risk of death or nonfatal cardiovascular events in patients undergoing dialysis with moderate to severe hyperparathyroidism. In the unadjusted intention-to-treat analysis, cinacalcet did not significantly reduce the risk of death or major cardiovascular events. Subsequent subgroup analysis showed that cinacalcet decreased the risk of death and major cardiovascular events in older, but not younger, patients on hemodialysis.

Vitamin D derivative (calcitriol) and synthetic vitamin D analogs bind to vitamin D receptors to increase intestinal calcium absorption and bone resorption, thus suppressing PTH. Vitamin D therapy should not be started until serum phosphorus has been controlled (< 5.5 mg/dL) and serum calcium is < 9.5 mg/dL because vitamin D increases intestinal absorption of calcium and phosphorus and promotes vascular calcification. There have been no prospective studies demonstrating that the use of vitamin D or its analogs has any effect on cardiovascular mortality.

Optimal Dialysis Prescription

Phosphate is distributed unevenly in various compartments of the body, with only a small amount in the plasma compartment and the majority in muscles, cell walls, and bone. Although hemodialysis can effectively remove phosphate, transferring phosphate from these spaces to the plasma is relatively slow. Standard hemodialysis (4 hours per treatment) removes approximately as much phosphorus as is absorbed in a single day. However, patients eat 7 days a week and are generally dialyzed 3 days a week. Phosphate clearance can be improved by increasing the frequency of the dialysis treatments. Several studies have shown that patients undergoing short daily or nocturnal dialysis had better phosphorus control and required a lower dose of phosphate binders. In PD, phosphate clearance may be influenced by PD modality (continuous ambulatory PD or continuous cycling PD) and membrane transport type.

Besides the use of calcium-containing binders and vitamin D, a high dialysate calcium concentration also contributes to positive calcium balance in patients on hemodialysis. In a crossover study, Basile et al. measured hourly ionized calcium with three different dialysate calcium concentrations (2.5, 2.75, and 3.0 mEq/L). They found that calcium balance was positive with all dialysate calcium concentrations and increased progressively with a higher dialysate calcium bath. The additional calcium influx to the patient transiently increases arterial blood ionized calcium, which suppresses PTH levels and induces bone mineralization. Once the bone becomes fully mineralized, the additional calcium contributes to calcification in soft tissue such as arterial media. In a randomized controlled trial, patients dialyzed against 1.75 mmol/L calcium bath had a faster progression of coronary artery calcification compared to those dialyzed against 1.25 mmol/L calcium bath. The KDIGO guidelines suggest using 1.25–1.50 mmol/L dialysate calcium bath as it results in a relatively neutral calcium balance in the majority of patients during dialysis.

Conclusion

CKD-MBD is a systemic disorder of mineral and bone metabolism manifested by abnormalities in serum calcium, phosphorus, PTH, and FGF23, as well as bone disease and extraosseous calcification. All of these abnormalities are associated with increased mortality in patients with CKD. Management of this complex disorder includes lowering dietary phosphate intake, administration of phosphate binders, use of calcimimetics, vitamin D, and appropriate dialysis treatments. In the past decade, there have been more data suggesting the potentially harmful effect of calcium-containing phosphate binders and use of high dialysate calcium concentrations on vascular calcification, which could contribute to the high cardiovascular mortality in patients with CKD.

Recommended Reading

Alem AM, Sherrard DJ, Gillen DL, et al. Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int.* 2000;58(1):396–399.

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Chen W, Bushinsky DA. Chronic kidney disease: KDIGO CKD-MBD guideline update: evolution in the face of uncertainty. *Nat Rev Nephrol.* 2017;13(10):600–602.

This editorial provides a brief overview of the 2017 KDIGO update on CKD-MBD.

Gutierrez OM, Mannstadt M, Isakova T, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med.* 2008;359(6):584–592.

Increased FGF23 levels appear to be independently associated with mortality among patients who are beginning hemodialysis treatments.

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Increased FGF23 levels are independently associated with all-cause mortality, cardiovascular events, and initiation of chronic dialysis in patients with advanced CKD.

Disease Kidney, Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline update for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKDMBD). *Kidney Int Suppl (2011).* 2017;7(1):1–59.

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This study determines the prevalence of phosphorus-containing food additives in best-selling processed grocery products and compares the phosphorus content of a subset of top-selling foods with and without phosphorus additives.

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This study demonstrates that the source of protein (vegetarian vs meat diet) has a significant effect on phosphorus hemostasis in patients with CKD.

Nickolas TL, McMahon DJ, Shane E. Relationship between moderate to severe kidney disease and hip fracture in the United States. *J m Soc Nephrol.* 2006;17(11):3223–3232.

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Rivara MB, Ravel V, Kalantar-Zadeh K, et al. Uncorrected and albumin-corrected calcium, phosphorus, and mortality in patients undergoing maintenance dialysis. *J Am Soc Nephrol.* 2015;26(7):1671–1681.

Using data from dialysis patients treated in DaVita, Inc., facilities, this study accessed the association of uncorrected and albumin-corrected calcium and phosphorus with mortality.

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Using data from the Dialysis Outcomes and Practice Patterns Study (DOPPS), this article describes international trends in calcium, phosphorus, and PTH levels over 10 years and identifies mortality risk categories.

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Phosphate Management in Patients with End-Stage Kidney Disease

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Introduction

Achieving adequate control of serum phosphate (P) is one of the most difficult challenges facing clinicians caring for patients with end-stage kidney disease. Despite the global acceptance of the consequences of elevated P and despite a large number of therapeutic options targeting this mineral disorder, almost no discernible progress has been made toward routinely achieving the international recommendation of a P level of <4.6 mg/dL. More than 80% of patients on dialysis receive phosphate binders, leading to a tremendous pill burden estimated at nearly 11 pills per patient per day, and yet, the proportion of patients achieving a serum P <5.5 mg/dL has *decreased* over the last decade, and nearly 80% of patients do not maintain a serum P <5.5 mg/dL over a 6-month period. Elevations of P are a key component of what is now commonly referred to as CKD-MBD (chronic kidney disease–mineral and bone disorder), a systemic disorder affecting the skeleton and vasculature and is consistently associated with an increased risk of all-cause mortality, cardiovascular (CV) mortality, and vascular calcification. A recent analysis of the Dialysis Outcomes and Practice Patterns Study (DOPPS) demonstrated that globally, fewer than 17% of patients achieve a P <4.6 mg/dL over a 6-month period. In this analysis, a time-averaged P of between 5.5 and 6.5 mg/dL was associated with a 40% increase in CV mortality, and a time-averaged P ≥6.5 mg/dL was associated with a doubling of CV mortality. Effective P control requires thoughtful attention to all aspects of phosphate homeostasis, including diet, dialysis prescription, control of secondary hyperparathyroidism (sHPT), and individualized prescription of medication to reduce intestinal phosphate absorption.

Phosphate Physiology

Phosphorus is the second most abundant element in the human body after calcium. Approximately 85% of phosphorus is located in bones and teeth, 14% is intracellular, and only 1% is extracellular. In normal adults, the fasting plasma phosphate concentration ranges from 2.5 to 4.5 mg/dL (0.80–1.45 mmol/L); however, the majority of healthy individuals have serum phosphate <4.0 mg/dL. This represents the net balance of daily dietary intake, intestinal absorption, skeletal influx/efflux, cellular redistribution, and urinary phosphate excretion. There is substantial diurnal variation in serum P even in patients on dialysis, with >1 mg/dL differences between nadir (8 a.m.–12 noon) and peak (3–5 a.m.). The recommended dietary allowance of phosphorus is 700 mg/day, whereas the average dietary intake according to nutritional database information ranges from 1000 to 1800 mg (18–36 mmol) per day. These estimates, however, substantially underestimate actual phosphorus intake by 35%–100% because they reflect only natural sources of phosphate and do not account for the routine use of phosphate additives in food processing. Substantial quantities of phosphate in the form of additives are found in commonly prescribed medications and common beverages. Foods high in phosphate are typically those also high in protein and include dairy products, meats, eggs, and cereal; however, the bioavailability of meat-based phosphate far exceeds that of plant-based phosphate because of the lack of naturally occurring phytase in the human gastrointestinal (GI) tract. Phosphate contained in food additives is essentially 100% absorbed, a fact that underlies the recommendation to encourage fresh and homemade foods for patients with CKD. Given the importance of maintaining adequate total protein intake (1.2 g/kg/day) in patients on dialysis, we concur with recommendations to go beyond the superficial assessment of total P content to evaluate both the bioavailability and P density (mg P/gram protein)—foods previously recommended to "avoid," such as nuts and legumes, have far less bioavailability and may be a part of an appropriate plant-based diet. Intestinal absorption of phosphate is greatest in the jejunum and ileum and occurs passively via a paracellular route and actively via a phosphate sodium-dependent cotransporter (NaPi-2b). Basal phosphate absorption is a linear, nonsaturable function of oral intake that is normally approximately

70% of ingested. Despite a reduction in circulating levels of 1,25(OH)-D3, intestinal P absorption is not reduced in CKD, suggesting that passive, paracellular P transport is the primary route of phosphate absorption. Phosphate-lowering therapy generally affects only the passive, nonregulated component of phosphate absorption, a finding likely underlying the unusual observation that all current phosphate-lowering therapies have similar clinical efficacy. Renal handling of phosphate occurs primarily by the regulation of proximal tubule expression of type II-a and type II-c sodium phosphate cotransporter (NaPi-2a/c). The daily filtered load of phosphate is approximately 4–8 g, and under normal conditions, only 5%– 20% of the filtered phosphate is excreted. Parathyroid hormone (PTH), 1,25(OH)D3, and fibroblast growth factor 23 (FGF-23) are key regulators of NaPi-2a/c expression and, thus, phosphate reabsorption in the renal proximal tubule. FGF-23 levels are extraordinarily elevated in patients receiving dialysis (10-1000X ULN), and FGF-23 has emerged as one of several plausible causative links between CKD-MBD and CV disease. Elevated serum FGF-23 levels consistently associate with adverse CV outcomes, particularly those related to incident congestive heart failure, sudden death, and more recently recognized infectious events. These adverse effects are complementary yet distinct from those seen with elevations in serum phosphate, which is universally recognized to accelerate the development of vascular calcification and subsequent arterial stiffening. It is of clinical relevance that dietary P load, serum calcium, calcium load, active vitamin D administration, and iron deficiency all stimulate production of FGF-23.

Phosphate-Lowering Therapy

There is a consistent body of literature to support the biologic plausibility of attempting to reduce serum P. Elevated phosphate levels are consistently associated with a variety of adverse outcomes in multivariable-adjusted analyses in patients with CKD-G5D, including all-cause mortality, CV mortality, and CV hospitalization. In the prospective observational COSMOS study of hemodialysis (HD) patients, optimal patient survival was observed at a P of 4.4 mg/dL. Recently, a novel approach to evaluating serum P control over time demonstrated that the time spent and the extent of elevation above a serum P $\geq$4.5 mg/dL were strongly associated with CV mortality. There are three methods to reduce phosphate exposure: dietary phosphate restriction, use of phosphate-lowering medication, and dialytic removal of P.

Dietary Phosphate Restriction

Dietary P restriction has traditionally been a mainstay of therapy; however, clinical trial data to support its efficacy in reducing serum P are limited. Intensive dietary counseling has been shown to reduce serum P over 6 months; however, a Cochrane analysis found limited overall support for the effect of dietary intervention on patient-level outcomes. Moe et al. have reported that despite equivalent total phosphorus content, significantly lower P exposure over 24 hours is observed with plant-based versus meat-based diets in patients with CKD. Current dietary recommendations emphasize the importance of the source of P (animal, plant, natural, or processed) rather than the total P content and in educating patients how to read food labels to identify phosphate additives. While not germane to its efficacy in patients requiring dialysis, the utility of dietary intervention is further confounded by recent data establishing that the historical "gold standard" of P intake and absorption, 24-hour urinary P, fails to reflect P absorption in patients with CKD and is rather a reflection of P retention. An interesting new line of research points to the potential role of gut dysbiosis in CKD as a potential modifier of MBD.

Dialytic Control of Hyperphosphatemia

Even with optimal dietary phosphorus compliance and appropriate use of phosphate binders in conjunction with conventional thrice-weekly HD (CHD), neutral phosphate balance is difficult to obtain. Aside from dialysis duration and frequency, the major determinants of dialytic phosphate removal are dialyzer surface area and predialysis serum phosphate level. This is in part due to the complex elimination kinetics of phosphorus. Within the first 60–90 minutes of initiation of HD, there is a rapid reduction in serum phosphate level, followed by a decreased phosphate gradient between the plasma and dialysate, resulting in less efficient transfer. Throughout the duration of the treatment, the rate-limiting step in phosphorus removal is the relatively slow movement of phosphorus from the intracellular pools to the extracellular pool. Rebound in serum P begins during the last hour of dialysis, with a large rebound occurring after the termination of dialysis, reaching 70%–80% of predialysis serum phosphate values. Phosphate removal with a standard 4-hour HD treatment ranges between 600 and 1200 mg (1800–3600 mg/week) and continuous ambulatory peritoneal dialysis averages 300–360 mg/day (2100–2520 mg/week). This amount is not substantially altered by use of different dialyzers, types of renal replacement therapy, or with the specific buffer used in dialysate. Short daily HD and nocturnal HD both enhance phosphate removal and, in some patients, allow for an increased dietary phosphorus intake with a decreased requirement for phosphate binders. Increasing dialysis frequency to improve P control is an appropriate therapeutic option reflective of the relationship between serum P and CV mortality. Hemodiafiltration is also associated with modest increases in net phosphate removal.

Phosphate-Lowering Medication

The availability of therapeutic choices that reduce paracellular passive P transport (NHE3 antagonists) or active P

transport (nicotinamide derivatives) demands a change in vernacular to a new term, *P-lowering medication*, that encompasses these new classes of drugs as well as traditional P binders. A variety of agents have been used to create poorly soluble phosphorus complexes in the intestinal lumen and, in doing so, limit passive phosphate absorption. These agents include aluminum salts, calcium salts, magnesium salts, nonabsorbed polymers, and iron-containing compounds. All these agents have demonstrated similar clinical efficacy in reducing serum phosphate in patients receiving dialysis; however, each may be associated with side effects and class-specific limitations. As expected, GI side effects are particularly common with intestinal phosphate binders.

Due to ethical considerations, there have been no randomized, placebo-controlled trials of P binders evaluating clinical endpoints; however, there have been three well-designed observational studies, DOPPS, accelerated mortality on renal replacement (ArMoRR), and COSMOS, which have reported significant survival benefits associated with phosphate binder use (independent of serum P), even after adjustment for nutritional status and other available confounding variables. Currently, an innovative large pragmatic randomized controlled trial (RCT) is underway evaluating two different P target values (High, $\geq$6.5 mg/dL or Low, $<$ 5.5 mg/dL), although it will not elucidate P binder class-specific harms or benefits.

Heavy Metal Compounds

Aluminum salts are highly effective phosphate binders, independent of pH. Unfortunately, despite limited total systemic absorption, clinical experience from the 1980s demonstrated that long-term use results in dementia, encephalopathy, microcytic anemia, and profound osteomalacia. Thus, in the United States, aluminum salts are typically rarely used and only as short-term therapy (4 weeks) when other means of controlling phosphate have failed. Like aluminum, lanthanum carbonate (LC) is a heavy metal that potently binds intestinal phosphorus, and that has minimal intestinal absorption, the result of which has not been demonstrated to result in clinical adverse effects. Unlike aluminum, it does not appear to cross the blood-brain barrier, and therefore, the potential for adverse neurologic effects is felt to be extremely low. Treatment with LC at doses of 500–3000 mg/day significantly reduces serum phosphate levels in a dose-related fashion, with a significantly lower incidence of hypercalcemia and elevated calcium $\times$ phosphorus product when compared with calcium-based binders. LC has an adverse-event profile similar to other phosphate binders, although it has clinically been associated with both diarrhea and intestinal obstruction, ileus, and fecal impaction. A long-term evaluation of safety found no increased risk of mortality or fractures with LC use, and a recent meta-analysis of nine RCTs in patients on HD reported a 55% reduction in all-cause mortality in those receiving LC as opposed to standard therapy.

Calcium-Based Compounds

After the discovery of the detrimental effects of aluminum-based binders, calcium-based binders became the most prescribed phosphate binders and, despite substantial clinical concern with safety, in many parts of the world, remain so today. Calcium carbonate and calcium acetate are widely available, relatively inexpensive, and effective at reducing serum phosphate. However, they have a lower affinity for phosphorus compared with aluminum compounds and hence require larger doses with an increased number of pills in order to achieve satisfactory control of phosphate. In addition, they result in a large calcium load, which is exacerbated by coadministration with active vitamin D compounds. Calcium acetate is composed of 25% elemental calcium and is effective across a wide range of intestinal pH, whereas calcium carbonate is 40% elemental calcium and is less effective at alkaline pH (as in patients receiving H2 blockers or proton pump inhibitors [PPIs]). Although current recommendations suggest limiting total daily calcium intake to 1500 mg/day (estimating 500 mg/day from the diet), few data exist to support the safety of this target. Two recent calcium balance studies in patients with CKD demonstrate a substantially positive calcium balance with doses of elemental calcium as low as 800–1000 mg/day. There is also no basis for the common practice of using serum calcium levels to ascertain the "safety" of using calcium-based phosphate binders. Calcium loading has been implicated in the molecular mechanism underlying vascular calcification (VC), promoting calcification through enhanced expression of the sodium and phosphate cotransporter Pit-1 on the surface of vascular smooth muscle cells and in stimulating FGF-23 production by osteocytes. Calcium-based P binders may further accelerate VC by impairing the absorption of vitamin K in the GI tract and thus reducing the activation of matrix Gla protein, an inhibitor of calcification. Additionally, calcium-based P binders increase the risk of hypercalcemia and are associated with the development of calcific uremic arteriopathy. Most importantly, they have now been demonstrated to increase mortality in two RCTs in CKD (as compared to sevelamer). Two recent meta-analyses reached similar conclusions demonstrating an increase in mortality associated with the use of calcium-based P binders. For these reasons, KDIGO now recommends restricting the dose of calcium-based P binders in all patients on dialysis, regardless of the presence or absence of other high-risk considerations. It is our opinion that calcium-based P binders should only be considered after all other therapeutic options have been exhausted.

Nonabsorbable Polymers

Sevelamer hydrochloride, now manufactured as sevelamer carbonate, was the first nonaluminum, non-calcium-based phosphate binder developed for the management of hyperphosphatemia in ESKD. This synthetic ion-exchange polymer is as effective as calcium-containing binders and is

generally well tolerated. Its major drawbacks are the large pill burden, GI side effects, and high cost. However, when compared to other phosphate binders, sevelamer has several "pleiotropic effects," including an anti-inflammatory effect, the ability to lower total cholesterol and low-density lipoprotein (LDL) cholesterol, and the ability to reduce uric acid levels. In randomized controlled clinical trials involving either prevalent or incident HD patients, sevelamer use was associated with a significant reduction in the progression of coronary artery and aortic calcification as compared to calcium-based binders. Similarly, a study in 466 CKD patients incident to dialysis showed a significant reduction in the risk of cardiac arrhythmias and all-cause mortality in patients treated with sevelamer versus calcium carbonate. A propensity-matched analysis of U.S. HD patients demonstrated a survival benefit associated with sevelamer use as compared to calcium-based phosphate binders, and two recent meta-analyses of P binders in CKD both report a significant survival advantage with sevelamer versus calcium-containing P binders. Bixalomer, a resin-based polymer similar to sevelamer, is available in Japan and has similar biochemical effects (reductions in P, PTH, and FGF-23).

Magnesium-Based Binders

An inverse relationship between serum magnesium and CV events in the general population suggests that magnesium may have a cardioprotective role, possibly mediated thru an effect on VC. In vitro data demonstrate that magnesium can interfere with calcium-phosphate crystal formation, and in vivo data using a 5/6 nephrectomy rat model confirms reduced VC with magnesium supplementation. In general, magnesium-based phosphate binders are less potent than most calcium salts and can have significant systemic magnesium absorption, resulting in increased serum magnesium levels. This may not be detrimental per se, given that observational data have demonstrated that mortality in dialysis patients is highest among those with the lowest serum magnesium. Combination magnesium carbonate (60 mg elemental magnesium)/calcium acetate (110 mg elemental calcium) (CaMg) has been approved for hyperphosphatemia management after it was demonstrated to have similar clinical efficacy to other phosphate binders with similar tolerability. Interestingly, this combination magnesium/calcium P binder has been shown to reduce (favorably) the serum propensity to calcify when measured ex vivo, and a 4-year prospective study in 138 HD patients demonstrated a significant reduction in pulse pressure, left ventricular mass index, and aortic valve calcification in those given CaMg as compared to sevelamer. Thus, experimental and clinical data support the notion that magnesium carbonate/calcium acetate effectively lowers serum phosphate and may attenuate VC progression.

Iron-Based Therapy

The prevalence of iron deficiency anemia in CKD-5D and the awareness of the risks associated with calcium-based phosphate binders have contributed to the development of alternative treatment options. It has been recognized for many years that iron-based compounds could effectively bind phosphate, and two such compounds are approved for the reduction of phosphate in patients on dialysis. Use of these agents is further driven by the recent recognition that iron deficiency stimulates an increase in FGF-23. Sucroferric oxyhydroxide (SFO) has been demonstrated to be as effective in reducing serum P as compared to active control (primarily sevelamer and calcium), but with a substantially reduced pill burden of fewer than four pills per day. This ability to reduce serum P effectively while substantially reducing pill burden has now been replicated in multiple trials, most notably in a large real-world effectiveness analysis of HD patients' newly prescribed SFO. No substantive change in systemic iron parameters is generally observed with SFO, although FGF-23 was reduced. Tolerability was comparable to active control, with the obvious exception of dark stools common to all iron preparations. As with all iron-based P binders, diarrhea is the most commonly reported adverse event.

Ferric citrate (FC), also known as ferric citrate coordination complex because the active ingredient is a mixture of various FC complex sizes, has a unique dual mechanism of action (MOA), which has served as the basis of approval for elevated serum P in patients on dialysis and iron-deficiency anemia in patients with CKD not yet on dialysis. In the registrational phase 3 clinical trials, FC was compared to active control over a 52-week trial period and demonstrated equivalent P control while simultaneously significantly increasing iron saturation and ferritin and simultaneously significantly reducing the use of ESA and intravenous iron. Tolerability was comparable to active control; however, there were significantly fewer serious adverse events, including a reduced hospitalization for CV, infectious, and GI reasons. The effect of FC on FGF-23 has been assessed in a number of clinical trials in patients with non-dialysis-dependent CKD and those receiving dialysis and consistently demonstrates reductions in FGF-23 by as much as 40%. The effect of FC on FGF-23 is almost certainly related to the effective treatment of iron deficiency, a known regulator of FGF-23.

Phosphate Transport Inhibitors

Several new or repurposed compounds are being investigated as future phosphate-reducing treatments that do not bind P but rather target active or passive intestinal P transport. Nicotinamide is a nicotinic acid derivative (and component of niacin) that in a rat model has been found to inhibit sodium-dependent phosphorus cotransport via the NaPi-2b transporter located in the intestinal brush border membrane. Several clinical reports have demonstrated the ability of nicotinamide to reduce serum phosphate in patients with CKD, although reduced platelet count has been reported as a potential complication. Indeed, in a 6-month RCT of 100 patients on HD comparing nicotinamide to sevelamer, a large number of patients randomized to nicotinamide withdrew due

to adverse events, including thrombocytopenia, with only 55% of subjects randomized to nicotinamide completing the study. Overall, nicotinamide- and sevelamer-treated patients had similar reductions in serum P. Accumulation of nicotinamide metabolites in CKD remains a concern. Tenapanor is a minimally absorbed inhibitor of the sodium-hydrogen exchanger type 3 (NHE3 inhibitor) under development for the treatment of elevated serum P. The mechanism of action by which tenapanor reduces P transport has recently been elucidated. By blocking NHE3, tenapanor results in a transient increase in intracellular [H+], which alters specific claudins within the tight epithelial junctions, reducing permeability to phosphate and reducing overall passive, paracellular P transport. As a result of this unique non-P-binding MOA, tenapanor is the first P-lowering therapy that does not require TID administration or administration with meals.

Phase 2 and 3 clinical trials utilizing BID dosing of tenapanor (10–30 mg BID) monotherapy have consistently demonstrated significant reductions in serum P and FGF-23. Due to the MOA that increases stool Na+, the primary adverse event reported with tenapanor is a transient increase in loose stool and an increase in stool frequency by approximately two bowel movements per week. Recent abstracts report significant improvements in the ability to achieve normal serum P with marked reductions in overall P-related pill burden with tenapanor.

Other Considerations

Several other factors must be considered when evaluating serum P in patients on dialysis beyond diet, provision of adequate dialysis, and the use of and adherence to P-lowering therapy. sHPT is a nearly ubiquitous consequence of CKD and it is well known that uncontrolled sHPT is both a cause, and a consequence of elevated serum P. Indeed, it was recently discovered that the key regulator of PTH synthesis and secretion, the calcium-sensing receptor, contains P binding domains that stimulate PTH, thus firmly establishing that P control is critical to effective PTH management. Similarly, data from patients postparathyroidectomy and dialysis patients given antiresorptive osteoporotic therapy conclusively demonstrate that the skeleton directly contributes to the observed elevated serum P. Finally, vitamin D receptor analogs (VDRAs) are the most commonly prescribed therapy for sHPT, and their effect on directly increasing active P transport in the GI tract and in stimulating FGF-23 cannot be overlooked. Elevated serum P is an acknowledged indication to use calcimimetic therapy preferentially to reduce PTH.

Recommendations

Given the substantial body of evidence in patients with CKD-5D associating phosphate levels above normal with a variety of important clinical outcomes, including increased all-cause and CV mortality, it is reasonable to continue to exert sustained effort directed at reducing serum phosphate when it is above 4.5 mg/dL. Beyond the direct benefits potentially anticipated with reduction in serum phosphate, there are emerging data that targeting the extremely elevated levels of FGF-23 observed in patients on dialysis may modify CV and infectious morbidity and mortality.

As a result, we recommend an approach to phosphate management in dialysis that integrates all aspects of CKD-MBD. Phosphate management must be viewed through the lens of improving outcomes meaningful to patients rather than laboratory values per se. The effects of therapy should consider consequences to other MBD lab variables, including Ca, P, PTH, and FGF-23. Specifically, we recommend:

- Optimal serum P is 4.0–4.5 mg/dL and serum P > 5.5 mg/dL should be avoided.
- Dietary education regarding P content and absorption characteristics of food sources (animal/plant/processed) and the impact of highly processed foods on serum P.
- Non-calcium-containing P binders should be used as first-line therapy for P lowering pending regulatory approval of other novel phosphate reducing agents.
- Calcium-containing P binder use should be restricted in all patients, and if used, the total amount of elemental calcium provided should not exceed 800–1000 mg/day. The clinical effectiveness and reduced calcium content of CaMg support this as the most reasonable calcium-containing P binder.
- Calcimimetic therapy should be considered first-line therapy for sHPT given its ability to reduce PTH effectively, Ca, P, and FGF-23.
- Increasing the frequency of dialysis is an appropriate intervention for persistently high serum P.

Recommended Reading

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Results of a 2-day symposium focused on the public health aspect of phosphate with a summary of the key information related to physiology and epidemiology.

Block GA, Rosenbaum DP, Yan A, Chertow GM. Efficacy and safety of tenapanor in patients with hyperphosphatemia receiving maintenance hemodialysis: a randomized phase 3 trial. *J Am Soc Nephrology.* 2019;30:641–652.

Results of a placebo controlled randomized trial demonstrating the efficacy and tolerability of a novel NHE3 inhibitor for P lowering.

Calvo MS, Uribarri J. Public health impact of dietary phosphorus excess on bone and cardiovascular health in the general population. *Am J Clin Nutr.* 2013;98:6–15.

Discusses data related to the use of phosphate additives in the food supply and the potential public health effects in those with normal renal function.

Di Iorio B, Bellasi A, Russo D. Mortality in kidney disease patients treated with phosphate binders: a randomized study. *Clin J Am Soc Nephrol.* 2012;7(3):487–493.

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41

Use of Vitamin D Sterols and Calcimimetics in Patients With End-Stage Renal Disease

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Disorders of bone and mineral metabolism in chronic kidney disease (CKD) begin early in the course of kidney disease as an adaptive response to maintain homeostasis, but progress affects multiple organs and functions as renal function decreases. These alterations known as CKD-mineral and bone disorders (MBDs) include derangement of calcium, phosphorus, parathyroid hormone (PTH), vitamin D, fibroblast growth factor 23 (FGF-23) metabolism, increase in bone fragility and fracture risk, and vascular calcifications leading to elevated morbidity and mortality due to cardiovascular disease.

As the glomerular filtration rate declines, phosphate levels are maintained by an increased phosphaturia induced by FGF-23. However, since there is also a deficiency of klotho, the coreceptor for FGF-23, PTH increases, but this is not sufficient to maintain phosphate levels. With CKD progression, hyperphosphatemia and FGF-23 inhibit 1-alpha hydroxylase in the kidney, resulting in a decrease in the synthesis of 1,25-dihydroxyvitamin D (calcitriol). Consequently, intestinal calcium absorption decreases, leading to hypocalcemia and a reduction in calcitriol-dependent regulation of PTH synthesis. These changes contribute to the development of parathyroid hyperplasia and progression of secondary hyperparathyroidism (SHP). Parathyroid cells under these conditions have a reduced number of vitamin D receptors (VDRs) and calcium-sensing receptors (CaSRs) and thereby become resistant to their natural regulators, calcitriol, and calcium.

The effective management of CKD-MBD requires interventions directed to regulate the altered mechanisms summarized earlier.

Management of CKD-MBD involves a multifaceted approach targeting the following:

1. Correction of hypocalcemia
2. Control of hyperphosphatemia by dietary restriction, the use of phosphate binders, and adequate dialysis
3. Administration of vitamin D sterols
4. Use of calcimimetics

Vitamin D sterols

Vitamin D sterols play a central role in the management of SHP by directly inhibiting PTH secretion and increasing calcium absorption in the gut, which favors correction of hypocalcemia. Calcitriol, the natural form of active vitamin D, is produced in the kidney from its precursor 25-hydroxyvitamin D. Synthetic active vitamin D sterols retain the PTH-lowering effect of calcitriol but have lower calcemic action due to a decrease in their effect on intestinal calcium absorption. These features confer an advantage to the synthetic analogs, particularly when the risk of hypercalcemia is elevated. Active vitamin D sterols include paricalcitol, alfacalcidol, doxercalciferol, 22 oxacalcitriol, and falecalcitriol. Only calcitriol, paricalcitol, and doxercalciferol are available for clinical use in the United States.

Low levels of 25-hydroxyvitamin D are frequently observed in patients with CKD. Since 25-hydroxyvitamin D is the substrate for calcitriol, it seems reasonable to administer native vitamin D, ergocalferol, or cholecalciferol, to correct vitamin D deficiency or insufficiency and increase the substrate for calcitriol. Supplementation with ergocalciferol has shown a trend to reduce PTH levels in patients with CKD stages 3 and 4. However, in patients with advanced CKD, native vitamin D may not be sufficient to overcome the reduced ability of the remnant kidney to produce calcitriol. Therefore, most patients will require active vitamin D analogs or calcimimetics to achieve an adequate suppression of PTH. Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend addressing modifiable risk factors for all patients, including hyperphosphatemia, hypocalcemia, and vitamin D status, and to follow trends of PTH elevation rather than single values to decide treatment with PTH-lowering agents.

Although numerous studies have demonstrated that active vitamin D agents are effective at lowering PTH levels,

their use is limited due to the risk of hypercalcemia. This appears to be less severe with analogs compared with calcitriol. However, the PRIMO randomized controlled trial, conducted to determine whether paricalcitol would have a beneficial effect on the left ventricular mass index in patients with CKD stages 3 to 4, showed a significantly increased risk of hypercalcemia without a beneficial effect on cardiac endpoints. Similarly, the OPERA study showed that oral paricalcitol improved hyperparathyroidism but did not affect left ventricular structure and function.

The efficacy of active vitamin D sterols in controlling SHPT in patients with CKD stages 3 to 5 and patients on dialysis have been extensively demonstrated, mainly with regard to biochemical endpoints. However, studies evaluating their end-organ effect are relatively scarce. In observational studies, a favorable effect on patient mortality has been associated with therapy with active vitamin D sterols. Few studies have shown improvement in bone histology.

In patients with CKD stage 5 on dialysis requiring PTH-lowering therapy, KDIGO suggests calcimimetics, calcitriol, and active vitamin analogs alone or combined. Initiation of therapy with either agent should be at low doses, with progressive increases to achieve the desired target PTH level. KDIGO recommends a range of intact PTH (iPTH) levels within 2 to 9 times the upper limit of normal for the PTH assay used. Trends in iPTH values should be carefully followed since wide deviations of iPTH values even within the target range may require adjustment of therapy. Limitations for the use of these agents are more frequently related to the development of hypercalcemia and hyperphosphatemia due to increased intestinal absorption. In these cases, adjustment of the dose and avoidance of calcium-containing phosphate binders are recommended. Another limitation of active vitamin D analogs is their limited effectiveness in reducing PTH to appropriate levels, particularly in patients with severe hyperparathyroidism and nodular parathyroid hyperplasia. In these cases, addition or switching to other agents such as calcimimetics may be of help.

Calcimimetics

The CaSR plays a central role in the regulation of PTH secretion. This receptor is highly sensitive to calcium and other substances known as calcimimetics. Calcimimetics bind to a site in the receptor, increasing its sensitivity to calcium, resulting in inhibition of PTH secretion at lower calcium concentrations. Studies in dialysis patients have shown that calcimimetics reduce PTH levels in a dose-dependent manner. In addition, they decrease serum calcium and phosphate levels. Currently, there are two calcimimetics approved for clinical use, cinacalcet and etelcalcetide. The efficacy of cinacalcet, which is administered orally on a daily basis, has been widely demonstrated. Of interest, calcimimetics have been effective in patients who did not achieve adequate reduction of PTH levels while on active vitamin D analogs due to the associated elevation of serum calcium and phosphate levels. Etelcalcetide is an intravenous calcimimetic with a longer half-life, which allows its use three times weekly after hemodialysis. Given their effect on PTH, calcium, and phosphate levels, calcimimetics can facilitate the control of hyperparathyroidism, help achieve practice guideline targets for iPTH, and are especially useful in patients with marginal or frank hypercalcemia or hyperphosphatemia. If hypocalcemia occurs, oral calcium supplements and vitamin D analogs may be given.

A study in hemodialysis patients with moderate to severe SHP randomized to cinacalcet or etelcalcetide demonstrated noninferiority of etelcalcetide compared to cinacalcet at achieving control of serum PTH and, in fact, showed superiority attaining greater than 50% reduction in PTH levels. A decrease in serum calcium is a relatively common side effect with both calcimimetics. Therapy with calcimimetics is often limited by nausea, which may lead to noncompliance with this therapy.

The ADVANCE trial, a randomized prospective study designed to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in CKD patients on hemodialysis, showed that coronary artery and valvular calcifications were significantly lower compared with those receiving vitamin D alone. The EVOLVE study, a multicenter prospective, randomized, placebo-controlled trial, showed an improvement in PTH levels in patients treated with cinacalcet but did not demonstrate significant differences in the risk of death or major cardiovascular events. Other studies have shown that etelcalcetide is effective in reducing iPTH levels, calcium, and phosphate, irrespective of the severity of SHP, but iPTH goals were better attained in patients who initiated treatment at the lowest levels of SHP severity.

Regarding end-organ effects of calcimimetics, prospective studies have shown that cinacalcet improves bone histology in dialysis patients, particularly high bone turnover and fibrosis, which are both due to hyperparathyroid bone disease. Adynamic bone disease, a condition frequently associated with PTH oversuppression, was observed in a few patients. Therefore, close follow-up of iPTH levels is recommended to avoid excessive suppression.

There are doubts as to how much reduction of iPTH should be attained. Thus, too high levels are associated with severe hyperparathyroid bone disease and cardiovascular morbidity and mortality, whereas excessive suppression of PTH levels is associated with adynamic bone disease. Since bone turnover is, to a great extent, a function of PTH, iPTH levels have been used clinically to guide therapy. The accuracy of biochemical bone markers to predict bone histopathology was recently analyzed in a large retrospective study in dialysis patients from different countries. It was observed that iPTH and bone-specific alkaline phosphatase allowed discrimination of low and high bone turnover, albeit sensitivity and specificity were not optimal. The best iPTH cut-off value to discriminate low from non-low bone turnover was 103.8 pg/mL, and the best cut-off for discrimination of high from non-high bone turnover was 323 pg/mL, consistent with the

recommendations of KDIGO and Kidney Disease Outcomes Quality Initiative (KDOQI). These results provide help as to when to start or stop treatment to avoid oversuppression of PTH or extremely high PTH levels that could lead to adynamic bone disease or uncontrolled hyperparathyroidism, respectively. It is important to keep in mind that bone turnover is not the only parameter to be considered in the assessment of bone disease in CKD. Indeed, as suggested by KDIGO, bone volume and mineralization are important to consider together with bone turnover to define the status of bone health and disease. The value of other biochemical bone markers in assessing bone disease in CKD remains inconclusive.

In conclusion, there is a close relationship between alteration of bone and mineral metabolism with bone fractures, vascular calcification, morbidity, and mortality in patients with CKD. As SHP is central in the pathophysiology of these alterations, an adequate control of PTH levels is important to reduce their impact. Active vitamin D analogs and calcimimetics, independently or combined, have demonstrated to be effective at reducing PTH levels. However, adequate control of PTH levels requires a simultaneous regulation of phosphate and calcium metabolism and regular monitoring of biochemical parameters. In this regard, individualized treatment plans should be established to ensure the best possible control so that potential risks are minimized.

Recommended Reading

Bellorin-Font E, Vasquez-Rios G, Martin K. Controversies in the management of secondary hyperparathyroidism in chronic kidney disease. *Curr Osteoporosis Rep.* 2019;17:333–342.

This article highlights controversial aspects about the therapeutic alternatives to treat CKD patients with SHP and suggests individualization of therapy for better results.

Block GA, Bushinsky DA, Cheng S, Cunninham J, et al. Effect of etelcalcetide vs cinacalcet on serum parathyroid hormone in patients receiving hemodialysis with secondary hyperparathyroidism. *A randomized clinical trial JAMA.* 2017;317:156–164.

This is a randomized, multinational, double-blind, double-dummy active clinical trial that compares etelcalcetide vs. cinacalcet or placebo on serum PTH in patients with SHP in hemodialysis. The study shows that both cinacalcet and etelcalcetide were effective at lowering PTH levels. Etelcalcetide was not inferior to cinacalcet, and even demonstrated superiority at decreasing PTH levels.

Chertow GM, Block GA, Correa-Rotter R, et al. E.T. Investigators. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med.* 2012;367(26):2482–2494.

A major trial of cinacalcet therapy in ESRD showing excellent control of hyperparathyroidism. This study was not definitive in demonstrating a mortality benefit.

Cunningham J, Block GA, Chertow GM, et al. Etelcalcetide is effective at all levels of severity of secondary hyperparathyroidism in hemodialysis patients. *Kidney Int Rep.* 2019;4:987–994.

This article analyzes data from two phase 3, randomized, placebo-controlled trials conducted in adult patients with SHP on dialysis. The study demonstrates that etelcalcetide lowers iPTH, calcium, and phosphorus, irrespective of severity of SHP and that the ability to obtain target goals was greatest when initiated among patients with less severe disease.

KDIGO. Clinical practice guideline update for the diagnosis, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD MBD). *Kidney Int Suppl.* 2017;2017(7):1–59.

This is an update of the CKD-MBD guideline published in 2009 and describes the current practice recommendations for prevention and therapy of CKD mineral and bone disorder.

Ketteler M, Martin KJ, Wolf M, et al. Paricalcitol versus cinacalcet plus low-dose vitamin D therapy for the treatment of secondary hyperparathyroidism in patients receiving haemodialysis: results of the IMPACT SHPT study. *Nephrol Dial Transplant.* 2012;27(8):3270–3278.

This trial compares paricalcitol with cinacalcet plus low-dose vitamin D for secondary hyperparathyroidism and shows that although both paradigms may be used successfully, the paricalcitol-based regimen provided superior control of iPTH.

Malluche HH, Monier-Faugere MC, Wang G, et al. An assessment of cinacalcet HCL effects on bone histology in dialysis patients with secondary hyperparathyroidism. *Clin Nephrol.* 2008;69:269–278.

This study analyzes the effect of cinacalcet or placebo on bone histomorphometry in dialysis patients with SHP before and after treatment. It was found that cinacalcet lowers PTH levels and reduced bone turnover and tissue fibrosis.

Martin KJ, Gonzalez EA. Long-term management of CKD-mineral and bone disorder. *Am J Kidney Dis.* 2012;60(2):308–315.

This paper describes a general approach to therapy of CKD-MBD and discusses the heterogeneity and approaches to these issues.

Raggi P, Chertow GM, Torres PU, et al. The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. *Nephrol Dial Transplant.* 2011;26(4):1327–1339.

This work examines the effect of cinacalcet on the progression of vascular calcification.

Sprague SM, Bellorin-Font E, Jorgetty V, et al. Diagnostic accuracy of bone turnover markers and bone histology in patients with CKD treated by dialysis. *Am J Kidney Dis.* 2016;67:559–566.

This study shows that PTH and bone-specific alkaline have the best discriminant ability, albeit suboptimal, to predict high or low bone turnover utilizing the KDIGO-recommended cut-off of less than 2 times the lower limit of normal and more than 9 times the upper limit of normal for the iPTH assay used.

Thadhani R, Appelbaum E, Pritchett Y, et al. Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. *JAMA.* 2012;307(7):674–684.

This trial evaluated the effects of paricalcitol on cardiac structure and function in patients with CKD.

42 Parathyroidectomy

MARIANO RODRIGUEZ, MD, PhD

The Development of Secondary Hyperparathyroidism in Chronic Kidney Disease Patients

Mineral homeostasis requires precise regulation, and the kidney plays a crucial role. Deterioration of renal function causes an alteration in the regulation of calcium (Ca) and phosphate (P). There are a number of hormonal changes aiming to correct Ca and P disturbances. The term "chronic kidney disease-metabolic bone disease" (CKD-MBD) includes all abnormalities of mineral metabolism in CKD, that is, biochemical alterations, renal osteodystrophy, and extraosseous calcifications.

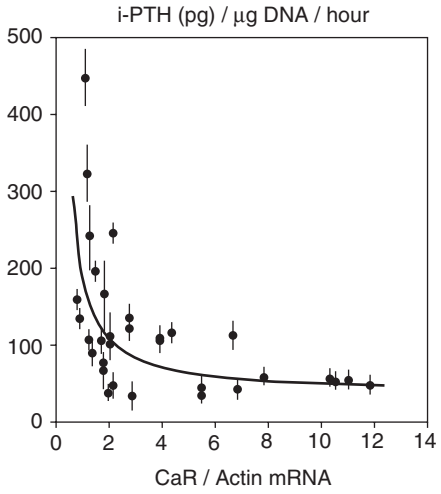
The parathyroid hormone (PTH) plays a central role in mineral homeostasis; small changes in serum Ca concentration levels are detected by parathyroid cells that are equipped with G-coupled Ca sensing receptor (CaSR). The activation of the CaSR by an increase in serum Ca reduces PTH secretion, and vice versa, a reduction in Ca stimulates PTH secretion. Intracellular signaling triggered by the CaSR will modify not only PTH secretion but also PTH synthesis and parathyroid cell proliferation. The increase in PTH corrects serum Ca levels by stimulating bone resorption with the consequent release of Ca and P to the extracellular space. In addition, PTH increases the synthesis of $1,25(OH)_2D3$ (calcitriol) by the kidney, which augments the intestinal absorption of Ca and P. PTH reduces calciuria through the stimulation of tubular reabsorption of Ca and also increases phosphaturia by reducing tubular reabsorption of P.

The parathyroid function is inhibited by high levels of Ca, 1,25D3, and FGF-23. Derangements in the levels of these elements constitute potent stimuli for the onset and progression of secondary hyperparathyroidism (SHPT).[1,2] One key factor in the development of SHPT is the accumulation of P due to the reduction of glomerular filtration. In CKD stage 3 and even 4, serum phosphate concentration is not increased because the increased P load stimulates the production of fibroblast growth factor 23 (FGF-23).[3] FGF-23 is produced by mature osteoblasts and osteocytes. It acts on the receptor FGFR1–Klotho complex, reducing the proximal reabsorption of P and also reducing calcitriol production by the kidneys. Therefore the P balance is maintained by the increased distal delivery of P, which is finally excreted in the urine. It has been shown that the increase in fractional excretion of phosphate reduces the expression of Klotho,[4] causing resistance to the action of FGF-23; thus, more FGF-23 has to be produced to maintain P excretion, and the demand for FGF-23 will continue unless oral P load is reduced. FGF-23 is found to be increased since the very early stages of CKD[5]; the progressive increase in FGF-23 produces a gradual decrease in calcitriol synthesis, which not only contributes to hypocalcemia but also deprives the parathyroid cell of the inhibitory effect of calcitriol. With CKD stage 4, the number of nephrons is reduced to the point that the increases in PTH and FGF-23 are not able to augment P excretion, then hyperphosphatemia, together with hypocalcemia, develops.

SHPT develops progressively in parallel with the continuous deterioration of renal function. It is characterized by elevated rates of PTH synthesis and secretion accompanied by parathyroid cell hyperplasia. Factors involved in the development of SHPT are hypocalcemia, hyperphosphatemia, and low 1,25D3 and FGF-23. Hypocalcemia and hyperphosphatemia stimulate PTH production and secretion[6–8] and promote cell proliferation. An important effect of P is the generation of skeletal resistance to the calcemic effect of PTH, which contributes to hypocalcemia with the subsequent stimulus for parathyroid hyperplasia.[9] Hypocalcemia increases the expression of proliferating cell nuclear antigen.[10–12] A direct stimulatory effect of P on PTH secretion was demonstrated 25 years ago.[6] Recent work by Centeno et al.[13] shows that high P concentrations act on specific elements of the CaSR to stimulate PTH secretion. Therefore, it is very difficult to manage SHPT without controlling serum P levels. A recent study by Kan et al.[14] examined signaling mechanisms involved in the development of parathyroid hyperplasia; low vitamin D levels activate nuclear factor kappa B (NFκB) in parathyroid glands. The absent or reduced antiproliferative action of 1,25D3[14] and the impaired regulation of p21 and αKlotho/FGF receptor (FGFR) signaling by FGF-23[15,16] contribute to the development of parathyroid hyperplasia. In animals with normal renal function, the elevation in FGF-23 causes a reduction in PTH production and cell proliferation, but as parathyroid hyperplasia

develops, there is a lower expression of parathyroid FGFR and Klotho receptors, which prevents any inhibitory effect of FGF-23.[15] In addition, there is a direct interaction between Klotho and CaSR that results in suppression of PTH synthesis and parathyroid proliferation.[17]

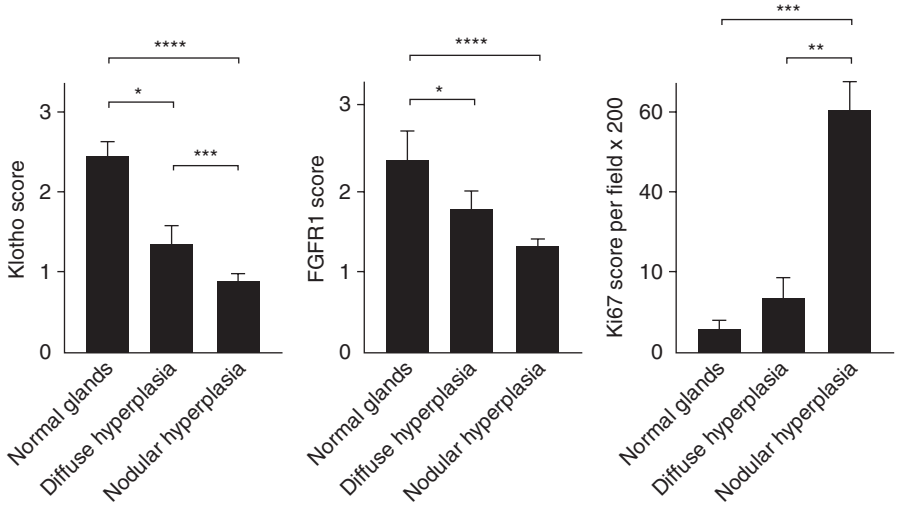
In hyperplastic glands, the expressions of vitamin D receptor (VDR), CaSR, FGFR1, and its coreceptor Klotho are markedly reduced. In addition, parathyroid adenomas show marked reductions in NFIL3 (nuclear factor, interleukin 3) and RET (rearranged during transfection).[18] Changes in microRNAs (miRNAs) are also involved in the pathophysiology of parathyroid hyperplasia, as shown by Shilo et al.,[19] who found high expressions of members of let-7, miR-30, and miR-141/200 miRNA families in parathyroid samples from humans, mice, and rats. In experimental hyperparathyroidism, the authors reported upregulation of miR-29, miR-21, miR-148, miR-30, and miR-141 and downregulation of miR-10, miR-125, and miR-25. This information may help to understand the development of SHPT better and may help in designing strategies to prevent parathyroid hyperplasia.



• **Fig. 42.1** The relationship between the in vitro basal parathyroid hormone (PTH) secretion *(i-PTH, (pg)/µg DNA/h)* and the calcium-sensing receptor expression *(CaR/actin-mRNA)* by human hyperplastic parathyroid tissue from patients with uremic hyperparathyroidism. The experiments were performed using tissue slices that were incubated for 1 hour in 1.25 mM Ca concentration. Data points are the mean ± SEM of two to four repeated experiments using different tissue aliquots from the same gland. (From Cañadillas S, Canalejo A, Santamaría R, et al. Calcium-sensing receptor expression and parathyroid hormone secretion in hyperplastic parathyroid glands from humans. *J Am Soc Nephrol*. 2005;16:2190-2197.)

Refractory Hyperparathyroidism

Parathyroid hyperplasia may progress from diffuse to nodular hyperplasia, which is characterized by a reduction in the expression of parathyroid receptors: CaSR, VDR, FGFR1, and Klotho. This is known as tertiary hyperparathyroidism, and at this point, the gland may be refractory to the medical treatment. Several research groups have reported that there is a decrease in CaSR in nodular areas.[20,21] Fig. 42.1 shows the in vitro PTH secretion in glands from patients with refractory SHPT (secondary hyperparathyroidism) incubated in normal calcium concentration; for the same ambient calcium, the PTH secretion is inversely proportional to the abundance of CaSR.[22] This explains the poor response to calcimimetics or the increase in Ca induced by 1,25D3 administration. Likewise, Fig. 42.2 shows the reduction of receptor FGFR1 in parathyroid glands with nodular hyperplasia.[23] The marked reduction in VDR density in nodular hyperplasia also contributes to the refractoriness to 1,25D3 treatment.[21] Studies performed in vitro using parathyroid gland tissue from parathyroidectomies performed in uremic patients demonstrate that there is an abnormal response to both Ca and 1,25D3 in nodular hyperplasia.[24,25]



• **Fig. 42.2** Semiquantification expression of Klotho, fibroblast growth factor receptor 1 *(FGFR1)*, and *Ki67* in parathyroid tissue of each group. The values shown are means ± SEM. *$p < 0.1$; **$p < 0.05$; ***$p < 0.01$; ****$p < 0.001$. (From Komaba H, Shunsuke Goto S, Hideki Fujii H, et al. Depressed expression of Klotho and FGF receptor 1 in hyperplastic parathyroid glands from uremic patients. *Kidney Int*. 2010;77:232-238.)

Indications for Parathyroidectomy

Parathyroidectomy (PTX) should be considered if medical therapy is ineffective in controlling PTH. Nowadays, with the introduction of new alternatives for medical treatment, mainly oral and intravenous (IV) calcimimetics, the indications could be reduced to:

- hyperparathyroidism refractory to treatment with calcimimetics
- severe refractory hyperphosphatemia
- severe SHPT (PTH > 800–1000 pg/mL without hypocalcemia) in dialysis without response to combined medical treatment (association of cinacalcet, P binders, and vitamin D derivates) for more than 12 months
- patients with calciphylaxis and PTH greater than 500 pg/mL who do not respond rapidly to treatment with calcimimetics
- complications associated with SHPT, such as tendinous rupture, severe bone pain, or refractory anemia
- primary hyperparathyroidism (non-iatrogenic hypercalcemia with nonsuppressed PTH) in patients with CKD (especially young patients)
- kidney transplanted patients with uncontrolled hypercalcemia with high PTH and poor response to calcimimetics

Important consequences of prolonged untreated SHPT are hip fracture and vascular calcification. Hip fracture is more than 85 times higher among dialysis patients younger than 45 years than in healthy persons of the same age. This cannot be ascribed solely to PTH, but its role is clearly contributory and, importantly, amenable to therapy. The prevalence of vascular calcifications is extremely high in end-stage renal disease.[26] Excessive elevation of PTH accentuates hyperphosphatemia, which produces osteogenic transdifferentiation of vascular smooth muscle cells.[27–29] In these cases, PTX may be an effective therapy that increases survival rates and patient quality of life.[30,31]

Surgical Management of Secondary Hyperparathyroidism

In the 1990s, Ca-containing P binders and calcitriol were increasingly used in the management of SHPT in dialysis patients in the United States. The PTX rate decreased from 11.6/1000 patient-years in 1992 to 6.8/1000 patients-years in 1998. From 1998 to 2002, with the advent of synthetic active vitamin D analogs and non-Ca-containing P binders, the use of calcitriol declined in favor of paricalcitol. However, the PTX rate increased to 11.8/1000 patients-years in 2002. In 2004, cinacalcet was introduced in the United States. In 2011 the rate of PTX was 4.9/1000 patients-years.[32]

Nowadays, technological advances allow performing surgeries efficiently with a very short hospital stay, less pain, and minimal scars.[33] Inhospital mortality rates after PTX for SHPT have steadily declined to < 1% in recent years.[34]

Subtotal Parathyroidectomy

This is the resection of three parathyroid glands and approximately half of the fourth, leaving between 40 and 80 mg of the most normal-appearing, well-vascularized parathyroid gland in situ. It appears preferable to save an inferior gland, more accessible to reoperation if necessary. Bilateral cervical thymectomy is performed to remove any supernumerary glands or parathyroid nests.[34] An extra (supernumerary) parathyroid gland in the thymus is usually identified by gammagraphic technique (technetium 99m sestamibi). Some experts consider subtotal PTX (sPTX) as a preferred approach in patients with moderate SHPT and a chance of short-term kidney transplantation. With a less aggressive parathyroid resection, a less severe decline in PTH should be expected, and the resection of the more abnormal parathyroid glands may be sufficient to normalize the serum Ca level.[34]

Total Parathyroidectomy With Parathyroid Autotransplantation

This includes resection of all four parathyroid glands with bilateral cervical thymectomy. The most normal-appearing gland is shredded into small pieces for reimplantation in muscle (sternocleidomastoid, brachioradial of the nondominant forearm) or the subcutaneous fat of the abdomen.[34] Recent advances have led to the development of total endoscopic (TPTX) + parathyroid autotransplantation (AT), with preoperative localization by parathyroid ultrasonography and highly-sensitive 99mTc-sestamibi radionuclide scans. A series of 34 patients with SHPT treated with TPTX + AT has been reported.[35] After 1.8 years, outcomes were excellent; calcium deposition in soft tissues either disappeared or was significantly decreased within 6 months after PTX. Only two patients developed (asymptomatic) postoperative hypocalcemia. Recurrence of SHPT occurred in one patient who had a fifth gland hidden behind the thyroid, which required a second resection.

A prospective randomized trial compared the outcome of sPTX or TPTX + AT in 40 patients equally distributed between both groups. This trial showed that compared with sPTX, TPTX + AT resulted in less recurrence and more success with normalization of serum Ca and alkaline phosphatase.[36] After sPTX, two patients required reoperation because of recurrent hyperparathyroidism originating from the remaining parathyroid gland in the neck, and another two patients were hypercalcemic at follow-up. In another retrospective study[37] of 46 dialysis patients comparing sPTX versus PTX + AT, it was found that postoperative calcium was similar with both procedures; the PTH was 32.6 (26.0) and 9.5 (4.2) in SPTX and TPTX + AT, respectively. Days in the hospital were similar. Reoperation was required in six SPTX patients and two TPTX + AT patients ($p = 0.12$). Long-term PTH < 15 pg/mL occurred in 5.6% of SPTX patients and 26.7% of TPTX + AT patients ($p = 0.09$). PTH values > 200 pg/L were observed in 38.9%

of SPTX patients versus 6.7% of TPTX + AT patients ($p < 0.05$). Calcium supplementation at more than 6 months was required for 36.8% of SPTX and 71.4% of TPTX + AT patients ($p < 0.05$). The long-term control of parathyroid hormone elevation and avoidance of recurrent disease are improved with TPTX + AT but carry a higher risk of long-term hypocalcemia.

Total Parathyroidectomy Without Autografting

Total PTX without AT and routine cervical thymectomy may provide an alternative strategy. A retrospective study compared TPTX + AT ($n = 504$), TPTX ($n = 32$), or sPTX ($n = 21$). Persistent hyperparathyroidism was rare in all three procedures; it occurred in 2/504 patients who underwent TPTX + AT (0.4%), no patients who underwent TPTX, and one patient who underwent sPTX. Postoperative levels of PTH were higher in the sPTX group (61.4 ± 12.6 pg/mL) than in the TPTX groups with or without AT (28.8 ± 3.1 and 27.0 ± 14.1 pg/mL, respectively). The authors concluded that TPTX with or without AT is the preferred surgical procedure.[38]

Total Parathyroidectomy Versus Parathyroidectomy With Autotransplantation

There are several recent studies aiming to compare TPTX versus PTX + AT. Schlosser et al.[39] evaluated a total of 52 patients who underwent TPTX and 48 patients who underwent TPTX + AT. Persistent SHPT developed in one TPTX and two TPTX + AT patients. Serum-calcium values were similar (2.1 ± 0.3 vs. 2.1 ± 0.2; $p < 0.95$). PTH in the TPTX + AT group was significantly higher at the end of follow-up (3 years) when compared with the TPTX group (31.7 ± 43.6 vs. 98.2 ± 156.8; $p < 0.02$). Recurrent SHPT developed in four TPTX + AT and none of the TPTX patients. It was concluded that TPTX + AT and TPTX seem to be safe and equally effective for the treatment of otherwise uncontrollable SHPT.

In a meta-analysis[40] including a total of nine cohort studies and one randomized controlled trial comprising 1283 patients, the authors show that compared with patients in the TPTX + AT group, patients in the TPTX group had lower rates of "recurrence" (odds ratio [OR] = 0.20, $p < 0.01$) and "reoperation due to recurrence or persistence" (OR = 0.17, $p = 0.002$), but higher risk of "hypoparathyroidism" (OR = 2.97, $P = 0.01$). However, none of the patients had developed permanent hypocalcemia or adynamic bone disease (ABD). The findings indicate that TPTX is superior to TPTX + AT for prevention of recurrent SHPT, and it seems to be a feasible alternative therapeutic option for the surgical treatment of refractory SHPT.

Another meta-analysis[41] found similar results. There were 10 cohort studies and one randomized controlled trial. There was no significant difference in surgical complications (relative risk [RR], 1.71; 95% confidence interval [CI], 0.77–3.79; $p = 0.19$), all-cause mortality (RR, 0.68; 95% CI, 0.33–1.39; $p = 0.29$), persistence of sHPT (RR, 3.81; 95% CI, 0.56–25.95; $p = 0.17$), or improvement in symptoms (RR, 1.02; 95% CI, 0.91–1.13; $p = 0.79$). As compared with PTX + AT, TPTX could reduce risk recurrence (RR, 0.19; 95% CI, 0.09–0.41; $p < 0.0001$) and reoperation (RR, 0.46; 95% CI, 0.24–0.86; $p < 0.01$). But TPTX increased the risk of hypoparathyroidism (RR, 2.63; 95% CI, 1.06–6.51; $p = 0.04$). The authors concluded that TPTX and TPTX + AT are useful methods for sHPT treatment and TPTX was superior for reducing the risk of sHPT recurrence.

Parathyroidectomy, Mineral Disease, and Mortality

Whether parathyroidectomized patients achieve optimal bone mineral disease parameters described by clinical guidelines has been addressed by different authors. In dialysis, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) clinical guidelines[42,43] recommend a target PTH of 150–300 pg/mL (16.5–33.0 pmol/L). The Kidney Disease, Improving Global Outcomes (KDIGO) guidelines[44] suggest maintaining serum PTH in the range of two to nine times the upper reference limit of the assay. The 2017 update of KDIGO guidelines emphasize that treatment of CKD-MBD should be based on the joint assessment of Ca, P, and PTH levels.[44]

Achieving Parathyroid Hormone Target

The proportion of patients achieving the PTH target suggested by the guidelines in the short-term group was 29%.[45] In the long-term group, 31% of patients had achieved the KDIGO target for PTH throughout the following 5 years.

Dynamics of changes in FGF-23 and Klotho levels after PTX have also been evaluated at 90 days. Takahashi and collaborators reported a marked and sustained decline in FGF-23 throughout the follow-up period, along with a decrease in Klotho on day 1, followed by an elevation afterward.[46] Wetmore et al. evaluated the changes in medication after PTX.[47] Not surprisingly, they reported an increase in the use of oral and IV calcitriol and Ca-based binders and higher dialysate Ca concentration, whereas the administration of IV paricalcitol and doxercalciferol, non-Ca P binders, and calcimimetic dropped after the surgery.

Bone Abnormalities

Uremic patients normally exhibit *bone abnormalities* due to the excessive resorptive activity of PTH, which improves following PTX.[48,49] Yet, PTH oversuppression may lead to an excessive reduction of bone activity and, therefore, to the development of ABD, characterized by skeletal pain and fractures.[50] Bone mineral density does increase following PTX[49], together with a histological improvement as assessed by bone histomorphometry.[48] Such changes appear to start

as soon as 1 week after the surgery.[51] The risk of fracture has been shown to be reduced in hemodialysis patients undergoing PTX compared with matched control subjects.[52]

Vascular Calcification

Vascular calcification, frequently observed in CKD patients, contributes to their high cardiovascular morbidity and mortality. The impact of PTX on calcification score was evaluated by Bleyer et al.,[53] who found a significant reduction ($p = 0.03$) in parathyroidectomized patients in comparison to controls. Calciphylaxis, a rare and perhaps related condition, is characterized by calcification of small cutaneous arteries and necrosis with extremely high mortality rates. Controlling elevated PTH is recommended in patients with calciphylaxis, and PTX may be useful for this purpose. In a study evaluating the influence of PTX on survival rate with calciphylaxis,[54] it was found that survival was higher in parathyroidectomized patients than in those who did not undergo surgery ($p = 0.007$).

It has been suggested that high PTH contributes to the progression of vascular calcification in hemodialysis patients.[55,56] High PTH (≥600 pg/mL) has been associated with increased mortality in hemodialysis for a variety of potential reasons, including the associated elevation of serum P and an independent effect of the PTH itself.[57] Hence the impact of PTX on survival has been extensively examined. Several studies support the beneficial effect of PTX on all-cause[58–66] and cardiovascular[61–65] mortality. This beneficial effect was confirmed in a systematic review and meta-analysis performed by Chen and collaborators.[67] PTX was associated with a reduction in both all-cause and cardiovascular mortality compared with medical treatment (28% and 37%, respectively). A study by Conzo et al.[68] showed no higher survival among parathyroidectomized patients, but this was a retrospective study with relatively few subjects.

Morbidity and Mortality

Several studies have addressed the issue of morbidity and mortality derived from parathyroid surgery. In an observational matched cohort study, Kestenbaum et al.[69] found that the 30-day mortality rate was increased in patients who underwent PTX ($n = 4558$) mainly due to cardiovascular and infectious causes; after 1 year, the trend was inverted. In a more recent study[70] involving 4435 hemodialysis patients, mortality related to the procedure was 2%; 9.8% of the patients died within 1 year after surgery, a relatively low rate suggesting that patients selected for PTX were otherwise healthier than the general dialysis population. In 90 dialysis patients who underwent PTX, Lim et al.[71] reported that four (4.4%) patients died within 1 year after surgery, the low rate again pointing toward favorable patient selection. Of the 25 hospital admissions for 14 patients over the 1-year post-PTX period, 36% were due to hypocalcemia or hypercalcemia.

Hungry Bone Syndrome

After PTX, the fast drop in PTH level produces a shift of calcium to the bone, causing hypocalcemia; this is called "hungry bone syndrome (HBS)." It occurs in up to 95% of PTX patients.[72] Several studies have evaluated the factors predisposing to postsurgical HBS.[73–75] Patients developing HBS were significantly younger than those who did not.[72–75] The probability of developing HBS is associated with high PTH and high ALP levels pre-PTX.[75] Likewise, the requirement of Ca replacement after PTX correlated significantly with presurgical levels of PTH, the fall in PTH, and alkaline phosphatase.[73] A low preoperative Ca is also a risk factor for the development of HBS,[74] and preoperative use of vitamin D did not prevent this outcome. As compared with the year preceding PTX surgery, the relative risk of hospitalizations with hypocalcemia was 17.1-fold higher.[70]

Complications of Parathyroidectomy

Persistent Secondary Hyperparathyroidism

Hyperparathyroidism may persist due to inadequate performance of the surgery, with a subsequent risk for reoperation. The rates of persistent SHPT reported in the literature vary widely, from 0.4% to 25%,[76] due to differences in surgical expertise, definitions, and follow-up. Recurrence was substantially higher (35%) in those cases when a gland was not found.[77] Thus, the main cause of recurrent hyperparathyroidism is the presence of supernumerary glands or abnormally located parathyroid glands. Supernumerary glands are present in 13%–14% of individuals,[78,79] and ectopic glands are estimated in 15%.[76] Technetium 99m sestamibi and ultrasound can identify ectopic parathyroid glands[79,80]; technetium 99m sestamibi plus single-photon emission computed tomography may improve diagnostic accuracy.[80] The half-life of intact PTH is short, and measurement of PTH during surgery predicts the success of PTX.[76,81]

Adynamic Bone Disease

Although PTX improves bone mineral density in uremic patients, one risk derived from parathyroid surgery is the development of ABD due to very low levels of PTH. ABD is characterized by low bone turnover with normal mineralization and without osteoid accumulation. Patients with PTH < 100 pg/mL are at high risk for developing ABD.[50,82–85]

A Final Remark

Despite the different pharmacological treatments for SHPT, it is not rare for patients to require PTX because medical treatment is ineffective. These patients most often have developed nodular hyperplasia with parathyroid glands that do not respond to VDR and CaSR activation. The opinion of this author is that some effort should be made to preserve

a small amount of parathyroid tissue with no evidence of uncontrolled proliferation. Leaving the body without any PTH may not provide the best long-term effects. Finally, this surgery is not free of complications, and risk-benefit considerations should always be evaluated in individual patients.

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43

Acquired Cystic Kidney Disease

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There are many types of cystic diseases of the kidney, but a specific form often occurs in end-stage kidney disease (ESKD) patients. *Acquired cystic kidney disease* (ACKD) is defined by the presence of four or more renal cysts for both kidneys and the absence of any hereditary renal cystic disease. These cysts are associated with potential complications, including significant bleeding and malignant neoplasms.

Epidemiology

ACKD is more commonly observed in men and those of African descent. Acquired renal cysts are found in fewer than 10% of predialysis patients with long-standing azotemia (serum creatinine > 2.5 mg/dL). However, the incidence increases to 10% to 20% after 1 to 3 years of dialysis and 90% or greater in those dialyzed for more than 8 to 10 years. These cysts have been reported in patients on either peritoneal dialysis or hemodialysis. Azotemia is the only consistent factor in the development of ACKD.

Pathophysiology

The pathophysiology of acquired renal cysts is uncertain, but numerous etiologic factors have been proposed, including ischemia, intratubular obstruction from casts or calcium oxalate crystals, and interstitial fibrosis leading to extratubular constriction and obstruction. These cysts form from tubules and often remain in communication with one or more tubular segments. The cysts are usually lined by a single layer of epithelial cells, which reveal an increased proliferative capacity, and some may demonstrate epithelial hyperplasia with tufting of the cells. All of these features are suggestive of increased tubular cell growth. The immunophenotype of most cyst-lining cells is often consistent with proximal tubular epithelial cells but can also consist of distal nephron epithelial cells. Cysts tend to be larger and more numerous and exhibit increased growth in males compared with females. Kidney transplantation reduces the incidence of ACKD because cysts can regress. ACKD can still occur in the native kidney of transplant patients, but the incidence is lower than that of dialysis patients.

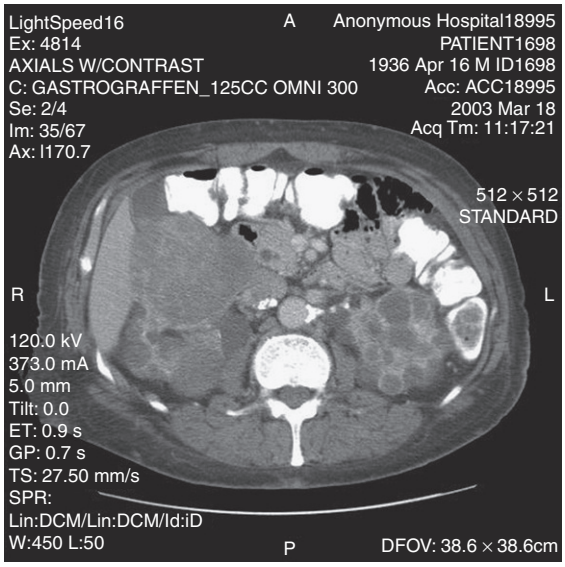
There are increased levels of inflammatory cytokines, including interleukin-6 (IL-6) and IL-8 and c-*jun*, in patients with ACKD. The proto-oncogene c-*jun* has been noted to be increased in early cyst formation associated with hyperplastic epithelium. Although c-*jun* activation was not noted uniformly in cystic kidneys with renal cell carcinoma (RCC), other specific growth factors remain to be identified. It is also known that cyst growth is increased by substances that stimulate cyclic adenosine monophosphate (cAMP) and that high levels of cAMP are found in dialysis patients, possibly as a response to parathyroid hormone (PTH). Other potential "renotropic factors" remain to be identified. Of interest, apolipoprotein L1 (ApoL1) is expressed in proximal tubular epithelial cells, and microcystic tubular dilation and thyroidization-type tubular atrophy were recently found to be fairly specific features in the kidneys of patients with two *APOL1* risk alleles (G1 or G2 variants). The specific role of ApoL1 has not been studied in ACKD, but given the increased incidence in those of African descent, this potential connection may be worth further consideration.

Clinical Course and Complications

The renal cysts of ACKD alone are not worrisome, and most patients (approximately 86% of all cases) are asymptomatic. ACKD can be complicated by episodes of kidney pain and urinary tract infections, but there are two important consequences with clinical implications. First, hemorrhage with hematuria due to cyst rupture/hemorrhage is the most frequent complication, occurring in 14% of ACKD patients, and a smaller subset of patients may develop perirenal or retroperitoneal hematomas or rarely renal rupture. Second, cysts with atypical features may represent the earliest precursor lesion of RCC. These ACKD-RCC-like cysts are lined by multiple cell layers with similar morphology and immunophenotype to the cells of ACKD-associated RCC but do not demonstrate areas of solid growth. Some ACKD cysts lined by a single epithelial cell layer also demonstrate the identical immunophenotype of concurrent neoplasms when present. Therefore, the risk of developing RCC in this population can be more than 100 times greater than in the general population with normal renal function, but overall,

this remains a rare complication with an annual incidence of less than 1%.

In the earliest reports, one-third of patients with cysts were found to have neoplasms. Most neoplasms were small, which were classified as renal adenomas based on their size (< 5 mm) and may be multifocal and bilateral. Larger neoplasms may represent RCC. There are two common subtypes of RCC in the setting of ACKD: (1) ACKD-associated RCC and (2) clear cell papillary RCC, which are both recognized by the 2016 World Health Organization classification of renal tumors. Other subtypes of RCC, such as conventional clear cell, papillary, and chromophobe, can also occur. Most ACKD-associated RCCs have favorable outcomes, but a subset is aggressive and demonstrates local recurrence or visceral and/or nodal metastasis, including the capacity for nodal metastasis at the time of diagnosis even when the primary mass is less than 3 cm in size, which contrasts with the other subtypes of RCC. Rare metastatic tumors have contained calcium oxalate crystals similar to the primary tumor, which can aid in diagnosis. Metastasis has also been associated with extended duration of hemodialysis (greater than 20 years). Some of these tumors may develop in the native kidneys of patients after kidney transplantation. Tumors have even occurred in pediatric patients who have been on dialysis for a prolonged period.



• **Fig. 43.1** Large acquired cystic kidneys with a large tumor in the right kidney. This tumor was found because of gross hematuria and was noted to be metastatic.

Diagnosis and Screening

Two imaging techniques have been the mainstays for detection of renal cysts. Ultrasonography is an easy, noninvasive method. However, end-stage kidneys are often shrunken and exhibit marked increased echogenicity, making cysts difficult to detect with ultrasonography. In addition, the low resolution of this technique may preclude the detection of small cysts and tumors (< 0.5 cm in diameter) often seen during the early stages of ACKD.

Although computed tomography (CT) scanning is more expensive and difficult to perform, it affords higher resolution, enabling detection of small cysts and tumors in shrunken kidneys. The intravenous (IV) administration of contrast material may further enhance tumor detection (Fig. 43.1). Helical CT with early enhancement rather than delayed enhancement may be superior in the detection of early tumors in ACKD. Magnetic resonance imaging (MRI) with gadolinium for further evaluation of complicated cystic renal lesions may be the best technique. However, nephrogenic systemic fibrosis is a potentially devastating complication of gadolinium use, so this particular compound is best avoided in patients with ESKD. When contrast is contraindicated, unenhanced MRI is recommended over unenhanced CT for evaluation of suspicious cysts. In children, European guidelines recommend ultrasound with selected use of MRI and contrast-enhanced ultrasound when malignancy is suspected. CT should be avoided in children due to radiation exposure.

Screening for ACKD and malignant neoplasms is controversial, and guidelines for dialysis patients have not been established. Schwarz and colleagues have recently suggested screening guidelines for kidney transplant patients. They recommend annual ultrasound imaging of native kidneys regardless of ACKD status. The frequency of ultrasound screening would increase with the complexity of renal cysts as detected by imaging. Screening for malignant neoplasms in ACKD patients is projected to achieve only a modest gain in survival over a 25-year period with significant economic costs and possible harm from imaging procedures because of radiation exposure. However, screening may be more beneficial in younger patients and those with fewer comorbidities and longer life expectancies. For this reason, patients are screened yearly in Japan, and the European screening recommendation for children on dialysis is an annual ultrasound exam. Other factors to be considered include the duration of azotemia (serum creatinine > 2.5 mg/dL for 3–5 years) and the length of time on dialysis. Special consideration should be given to patients awaiting renal transplantation. All such patients should be screened for ACKD and tumors, regardless of the duration of azotemia or dialysis. This screening will identify those patients with tumors before instituting active immunosuppression therapy.

The onset of symptoms such as hematuria or flank pain in a dialysis or chronically azotemic patient should lead to a prompt investigation for ACKD. Males with acquired cysts may need evaluation more frequently.

Treatment

Only a small proportion of ACKD patients develop significant complications. Hemorrhage into cysts or the collecting system is the most common. Usually, this bleeding requires only pain control. Aspirin should be avoided. If bleeding persists or becomes severe, wire-loop embolization remains

an option. A similar conservative approach is used for the treatment of retroperitoneal hematomas, although nephrectomy may be needed for uncontrollable hemorrhage or intractable pain.

Nephrectomy is the usual treatment for RCC in the setting of ACKD. However, nephron-sparing surgeries (radiofrequency ablation or cryoablation) and even active surveillance are gaining acceptance, especially in patients who may be poor surgical candidates. Nephrectomy should also be performed in all patients with tumors of any size who are candidates for renal transplantation.

Suggested Reading

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ACKD-associated and clear cell papillary renal cell carcinoma are common subtypes in ESRD patients, but other subtypes, including clear cell, chromophobe, and papillary, can also be encountered.

SECTION 5

Management of Co-Existing Illnesses and Special Populations

44

The Challenges of Blood Pressure Control in Hemodialysis Patients

PETER NOEL VAN BUREN, MD

Introduction

Hypertension is a risk factor for chronic kidney disease (CKD) that increases in prevalence as CKD progresses, and it is nearly universal in patients with kidney failure. The hemodialysis (HD) procedure itself induces hemodynamic changes throughout the course of treatment that warrant routine pre-, post-, and intradialytic blood pressure (BP) monitoring for safety purposes. Consequently, this generates an abundance of highly variable data between and within patients that make interpretation of cardiovascular and mortality risk as well as decisions on management very challenging. Compared to the general adult population and even patients with CKD, evidence-based guidelines for both BP targets and even specific pharmacologic antihypertensive therapy are lacking in HD patients. The purpose of this chapter is to present the unique challenges associated with the diagnosis and management of hypertension in HD patients. This includes emphasis on the role of extracellular volume (ECV) overload in this population, the significance of intradialytic and interdialytic BP changes, and discussion related to the pharmacologic treatment of hypertension in HD patients. While uncertainty exists for specific guidelines in many circumstances, this chapter provides some strategies for how to address frequently occurring situations that are independently associated with harm and other important considerations for managing hypertension in HD patients. The primary focus of the chapter is on the majority of HD patients that receive standard thrice-weekly in-center HD.

Pathophysiology of Hypertension in Hemodialysis Patients

Hypertension is present in approximately 30%–50% of the general population, but its prevalence is disproportionately higher in patients with CKD and greater with each incremental stage of CKD. Among patients with kidney failure, nearly 90% have hypertension (defined by systolic BP > 140 mm Hg or use of an antihypertensive drug) with little difference in distribution between varying demographics based on age, sex, race, or ethnicity. There are numerous mechanisms that contribute to the high prevalence of hypertension in this population (Table 44.1), and the unifying result is that they act to increase cardiac output, vascular resistance, or both. The overlap of many of these mechanisms may also explain why it is difficult to manage hypertension by targeting a specific individual process alone. ECV overload is a critical factor in hypertension in HD patients, so for the sake of this chapter, we will consider it separately after reviewing other mechanisms that are not related to ECV overload.

Factors Not Related to Extracellular Volume Overload

Sympathetic nervous system hyperactivity has been proposed to be one important mechanism contributing to hypertension in patients with kidney failure. This is based on the higher rate of postganglionic sympathetic-nerve discharge from the peroneal nerve observed in kidney failure patients compared to controls. It is of interest that a kidney transplant does not necessarily reduce sympathetic nervous system activity, but nephrectomy does. This suggests that the primary stimulus for the increased activity is likely not related to uremic toxins but rather signaling from the native kidneys. While adrenergic receptor blockers are not considered first-line therapies for patients in the general population, there is interest in how some of these agents might be particularly beneficial in HD patients (see later section on "Pharmacologic Antihypertensive Use").

Increased activity of the renin-angiotensin system (RAS) is another factor proposed to be responsible for hypertension in HD patients. Failing kidneys can still secrete renin even in the context of impaired glomerular filtration rate, and individuals with advanced kidney disease have inappropriately

TABLE 44.1 Mechanisms Contributing to Hypertension in Hemodialysis Patients

Excessive sympathetic nervous system activity
Excessive activity of the renin-angiotensin aldosterone system
Endothelial cell dysfunction (Imbalance between endothelin-1, asymmetric dimethylarginine, and nitric oxide)
Vascular stiffness
Oxidative stress
Exogenous pressor effects (erythropoetin stimulating agents)
Dialyzability of antihypertensive drugs
Extracellular volume overload

elevated levels of RAS activity given the relative degree of ECV overload. Before the era of targeted pharmacologic RAS inhibition, there was evidence that (1) at least a subset of hypertensive HD patients had hypertension that was strongly associated with circulating levels of RAS mediators, including renin and angiotensin II, and (2) there was a strong correlation between reductions in these mediators and BP following bilateral nephrectomy. Inhibitors of the RAS system are first-line agents in the general population and remain frequently prescribed for HD patients, although the specific long-term benefits in this population are less clear (see later section on "Pharmacologic Antihypertensive Use").

While the RAS mediator angiotensin II can induce vasoconstrictive effects by binding to receptors on vascular smooth muscle cells, vascular tone is further influenced by endothelial cell-derived mediators, including the vasoconstrictors endothelin-1 (ET-1) and asymmetric dimethylarginine (ADMA). ET-1 is released from endothelial cells, while ADMA is an endogenous inhibitor of nitric oxide synthase and can interfere with nitric oxide-induced vasodilatation. There is limited direct evidence of the hypertensive effects of these mediators in HD patients, but there is evidence that ADMA is significantly elevated in kidney failure patients and associated with higher cardiovascular events and mortality in this population. In addition to the worsening of endothelial cell function that may occur in HD patients as a comorbidity, there is also concern that the commonly prescribed erythropoietin stimulating agents may contribute to hypertension by increasing release of ET-1.

A separate concern related on the vascular biology of kidney failure patients is the potentially irreversible effects to blood vessels that can result from bone mineral disease. The combined calcium-phosphorus product has been associated with higher mean arterial pressure in HD patients. Hyperphosphatemia can contribute to vascular medial calcifications, and vascular calcification of various arterial beds is exacerbated by exposure to exogenous calcium through either the dialysate or calcium-containing phosphorus binders. There are likely multiple mechanisms to explain these associations, but poorly controlled renal osteodystrophy, in general, is likely yet another contributing factor to hypertension in HD patients.

Finally, an HD patient's response to various pharmacologic antihypertensives may vary greatly compared to those with normal or less severely impaired kidney function. In addition to consideration of the kidney clearance of medications that may vary, one must consider the dialyzability of the individual drugs, which can even vary within the same drug class. As with other toxins and medications, the dialyzability will depend upon factors related to molecular weight, protein binding, and water solubility. In short, either excessive or insufficient levels may result due to severely impaired glomerular filtration rate and the thrice-weekly dialysis schedule itself.

Extracellular Volume Overload

ECV overload is one factor that is particularly important and unique in the kidney failure population because these patients have lost most, if not all, ability to excrete sodium and water naturally through the kidneys. These circumstances predispose dialysis patients to ECV overload and make them largely reliant on the dialysis procedure to treat it. The patients go through phases of acute ECV expansion during each interdialytic period, and they can develop chronic extracellular overload if the appropriate target weight is either not identified correctly or is not able to be achieved due to limitations of fluid removal during dialysis.

The initial increase in BP from acute ECV expansion is likely due to increased cardiac output, but persistence of the volume expanded state can ultimately sustain high BP through a delayed increase in vascular resistance. In prevalent HD patients, the overall BP burden between dialysis treatments is more strongly associated with chronic ECV overload than it is with the acute interdialytic weight gains. Gradual dry weight lowering reduces both intradialytic BP and ambulatory BP as further support to the critical importance of controlling volume in order to control BP.

While ECV overload and hypertension can frequently coexist, it is important to acknowledge the independent effect of ECV overload on outcomes. Using either biomarker such as brain natriuretic peptide or bioimpedance spectroscopy to define ECV overload, there is evidence that patients who are more volume overloaded have higher mortality risk compared to patients who are more euvolemic. For any given range of systolic BP, the presence of ECV overload is associated with higher mortality risk. Because of this independent association, the lack of evidence-based guidelines supporting a specific BP target (discussed in detail later), and the influence of ECV management on intra- and interdialytic blood patterns, it is advisable to emphasize cautious but persistent optimization of ECV in HD patients to help stabilize BP and possibly improve outcomes in general.

Blood Pressure Targets in Hemodialysis Patients

Although hypertension becomes more prevalent as kidney disease progresses in patients, the management strategies for patients with and without advanced CKD are not exactly the same. There is evidence of a linear relationship between mortality and systolic BP in the general population, but there has consistently been shown to be a U-shaped curve that defines the relationship between BP measured before or after dialysis with mortality in HD patients. The Systolic Blood Pressure Reduction Intervention Trial identified the superiority of a target systolic BP < 120 mm Hg compared to 140 mm Hg among individuals with hypertension and at least one additional cardiovascular risk factor using the primary composite outcome of multiple individual cardiovascular endpoints and death from any cause. There were no kidney failure patients in this trial, but 28% had CKD. There were no differences between the two study arms in the occurrence of the primary endpoint among the CKD subgroup, but subsequent analysis identified that intensive BP lowering reduced mortality in the CKD participants. The current recommendation from the American Heart Association for patients with CKD is to target a BP of 130/80 mm Hg. Presently, there is no such trial with conclusive evidence of an ideal BP target in HD patients. The Blood Pressure in Dialysis (BP in HD) Trial was a pilot study investigating the effects of targeting a pre-HD systolic BP of 110–140 mm Hg compared to standard control (155–165 mm Hg) that found no difference in cardiovascular endpoints but increased risk of access thrombosis, hospitalization, and hypotension in the intensive group. While this study fails to identify an ideal target for predialysis BP, its results may not necessarily be generalizable for strategies that target *post-HD* BP targets. The current existing guidelines from the Kidney Disease Outcomes Quality Initiative recommend targeting a predialysis BP of 140/90 mm Hg or a postdialysis BP of 130/80 mm Hg. These recommendations likely stemmed from observational data that incremental increases in BP above these thresholds are associated with a higher risk for de novo congestive heart failure or coronary artery disease.

These recommended targets can be challenging to achieve, and they also fail to address the larger context of BP in this patient population with regard to the frequent BP changes that occur both during and between HD treatments. There are peridialytic and intradialytic BP patterns/behaviors that are now recognized as being associated with greater underlying cardiovascular risk and poor general prognosis. Several large epidemiologic studies show a U-shaped curve for the association between *change* in BP from pre- to post-HD and mortality, demonstrating a poor prognosis from large decreases in BP or *any increase* in BP from pre- to post-HD. Independent of these peridialytic measurements, the frequent occurrence of intradialytic hypotension during the treatment is also associated with higher mortality. So even when pre or postdialysis BP targets are achieved, the presence of intradialytic hypotension or intradialytic hypertension should alert clinicians that the patient has high-risk features that warrant consideration of modifying the management. Attempts should also be made to ascertain BP outside the dialysis unit with ambulatory BP monitoring or intermittent home BP measurements as these provide superior prognostic information regarding mortality and end-organ damage compared to pre and postdialysis measurements. If measurements from outside the dialysis unit are not available for review, one can increase the accuracy of predicting the ambulatory BP by considering the average of *all* intradialytic and peridialytic BP measurements.

We will discuss these specific challenges in BP management in HD patients in greater detail following a brief discussion on the "typical" response to an HD treatment.

Typical Hemodynamic Response to a Hemodialysis Treatment

BP frequently changes in most HD patients during and between dialysis treatments. High predialysis BP is in part a reflection of the recent interdialytic weight gain. In most patients, the HD procedure will induce a dual-sloped decline in BP where there is a steep decrease in BP during the first hour of the treatment that is then followed by a less steep decrease that continues for the remainder of the treatment. The volume or rate of fluid removal is associated with the BP slope during this latter portion of the treatments but not the initial portion of the treatment. A potential explanation for this initial ultrafiltration-independent decrease in BP is the effect of decreasing serum osmolarity. One observational study identified that the higher the level of calculated predialysis osmolarity, the larger the decrease in BP during dialysis. While the differences in intradialytic BP decrease between tertiles of predialysis osmolarity were low in magnitude, there was additional evidence that the predialysis urea level was independently associated with the occurrence of intradialytic hypotension, defined as a systolic BP nadir of 90 mm Hg or a reduction from predialysis BP of more than 30 mm Hg. Potential mechanisms for this observation could be related to either egress of fluid from the extracellular space (including the intravascular space) to the intracellular space or more rapid decreases in circulating vasoconstrictor vasopressin as the extracellular osmolarity decreases from rapid solute removal. The latter hypothesis was supported in part from a study randomizing patients to standard dialysis or biofeedback dialysis where the biofeedback dialysis resulted in higher serum sodium levels but blunted reduction in osmolarity and vasopressin at various points in time during dialysis. Another study identified significant differences in the intradialytic change in plasma osmolarity among patients with intradialytic increases in BP compared to those with intradialytic decreases in BP.

However, during the majority of the HD treatment, the rate of BP decline is associated with the amount and rate of ultrafiltration. Specifically, faster ultrafiltration rates and

larger ultrafiltration volumes are associated with a more rapid decrease in BP during dialysis. This critical concept underlines one of the prominent challenges in BP control in HD patients: minimizing ECV overload while simultaneously avoiding *intradialytic hypotension*.

Intradialytic Hypotension

Modest BP reductions during dialysis can be helpful in controlling overall BP burden in some hypertensive patients, but the extreme manifestation of this, known as intradialytic hypotension, should be avoided. Some of the risk factors associated with a higher likelihood of intradialytic hypotension are shown in Table 44.2. There are conflicting results on the effects of antihypertensive use on intradialytic hypotension, likely due in part to indication bias and the avoidance of various medications (calcium channel blockers, nitrates, etc.) in susceptible patients.

The definition of intradialytic hypotension has varied in the literature over the years, and one epidemiologic study identified that the frequent occurrence (>30% of treatments) of a nadir systolic BP <90 mm Hg was the most consistently associated with mortality compared to other definitions, including absolute systolic BP reductions (up to 50 mm Hg) and absolute decreases in systolic BP associated with intradialytic symptoms. For patients whose predialysis, systolic BP is at least 160 mm Hg, a systolic BP nadir <100 mm Hg was the definition most strongly associated with mortality. Another large study that was done in only incident dialysis patients found that mean nadir systolic BP <90 mm Hg or between 90 and 100 mm Hg was associated with higher 1-year, 2-year, and 5-year mortality compared to nadirs in the 110–120 mm Hg range, but this study also showed higher risk associated with high (>140 mm Hg) systolic BP nadirs. The study also found a U-shaped curve defining the adjusted association between delta systolic BP and mortality with decreases in systolic BP <15 mm Hg or >50 mm Hg having the highest risk. This latter study confirms the risk of low systolic BP nadirs (90–100 range) but also highlights the potential risk of intradialytic *hyper*tension (discussed further later). Finally, this and the previously mentioned study identified an escalating risk for mortality the more often that intradialytic hypotension occurs.

TABLE 44.2 Risk Factors for Intradialytic Hypotension

Underlying Risk Factors	Treatment-Related Factors
Older age	Faster ultrafiltration rate
Female sex	Shorter dialysis treatment time
Longer dialysis vintage	Higher dialysis temperature
Use of tunneled central venous catheter for vascular access	Lack of diuretic use
Presence of diabetes mellitus	
Presence of cardiovascular disease (coronary artery disease or congestive heart failure)	
Lower serum albumin	
Larger interdialytic weight gain	

The association between intradialytic hypotension and mortality is likely mediated through multiple organs and organ systems, including the heart, gastrointestinal tract, and central nervous system. For example, many HD patients may experience regional wall motion abnormalities of the left ventricle during dialysis. These events might be isolated to the dialysis procedure alone, but they can also persist after dialysis (which is referred to as myocardial stunning), which is associated with higher risk for progression of heart failure and mortality. Factors shown to be associated with regional wall motion abnormalities include higher ultrafiltration volume, larger intradialytic reductions in systolic BP, and overall lower nadir systolic BP. As cardiovascular disease, in particular sudden death and arrhythmias, is the leading cause of mortality in HD patients, the association between intradialytic hypotension and regional wall motion abnormalities provide clinicians with a potential target to avoid in routine clinical practice.

There may also be an association between intradialytic hypotension and one manifestation of the second leading cause of mortality in kidney failure patients: infection. Hypoperfusion of the gastrointestinal tract is a potential complication of intradialytic hypotension, and there is evidence that patients with intradialytic hypotension have higher levels of circulating endotoxin compared to those who do not have intradialytic hypotension. There is also evidence that admission to the hospital for mesenteric ischemia is often preceded by frequent episodes of intradialytic hypotension in the preceding month. Other concerning nonfatal consequences of intradialytic hypotension include those related to a decline in cognitive function from cerebral hypoperfusion, although it is likely that this may occur at absolute BP reduction or nadir BP thresholds that do not even meet the true definition of intradialytic hypotension.

As shown in Table 44.2, there are multiple risk factors for intradialytic hypotension related to patient-based factors, behavior-based factors, and treatment-related factors. It is important to recognize that the pathophysiology of intradialytic hypotension is likely different in different patient populations. One study using real-time assessment of hemodynamic parameters showed that intradialytic hypotension was as likely to be caused by a primary reduction in cardiac power index as it was a primary reduction in vascular resistance.

Because it may be difficult to ascertain the immediate etiology of a hypotensive episode, certain measures should be considered to minimize its risk. Much attention has been recently directed to the harm of rapid ultrafiltration rates

during dialysis. Similar to intradialytic hypotension itself, faster ultrafiltration rates have been associated with regional wall motion abnormalities and higher levels of circulating endotoxin after dialysis. Rapid ultrafiltration rates have also been associated with higher mortality, although the exact threshold where harm occurs is difficult to specify. One study including more than 1800 dialysis patients showed that an ultrafiltration rate > 13 mL/kg/h was associated with higher all-cause and cardiovascular mortality compared to a rate of < 10 mL/kg/h, with evidence of higher all-cause mortality at 10–13 mL/kg/h among patients with congestive heart failure. That study showed an inflection point where mortality started to increase around a threshold of 10 mL/kg/h, but an even larger study of around 100,000 patients subsequently showed that there were incremental increases in mortality risk starting at thresholds as low as 6 mL/kg/h. The higher risk from rapid ultrafiltration rates permeated across differing strata of body weight and body size, but the effect tended to be more pronounced among the larger patients.

Both the dialysis time and the ultrafiltration volume determine the ultrafiltration rate, are independently associated with mortality, and can be parameters to modify in the dialysis prescription. Specifically, limiting the interdialytic weight gain or lengthening dialysis time are appropriate strategies to minimize ultrafiltration rate. Practically speaking, dialysis adherence must be optimized to ensure that there are no intermittent episodes of excessively large interdialytic weight gain. Dietary sodium and fluid restriction are practices that should be reinforced to patients regularly, even when treatments are not missed. Pharmacologic interventions that might have beneficial effects on interdialytic weight gain include the use of high-dose diuretics to augment diuresis in patients with residual kidney function and medications to help control hyperglycemia in diabetic patients, which may limit thirst driven by hyperosmolarity. A controversial topic is the role of dialysate sodium as lower dialysate sodium prescriptions may be associated with less interdialytic weight gain, but themselves may be associated with higher hospitalization and mortality. In carefully selected patients (those with excessive weight gains but not frequent intradialytic hypotension), cautious lowering of dialysate sodium might be considered to limit thirst and fluid intake between dialysis treatments.

The other part of the equation determining ultrafiltration rate is the dialysis time. Longer dialysis treatments or additional treatments (either HD or ultrafiltration only) might be considered to limit the fluid taken off in any individual treatment. Intermittent additional treatments remain an option in patients who routinely undergo thrice-weekly dialysis, and consideration of alternative dialysis schedules is discussed further later.

In some patients, intradialytic hypotension might occur due to vascular resistance decreases or insufficient compensatory vascular resistance increases and might be more difficult to avoid by simply focusing on different fluid removal strategies. Lowering the temperature of the dialysate has been shown in a meta-analysis to have a beneficial effect on intradialytic BP, but long-term benefits are unknown. Midodrine is an alpha-adrenergic receptor agonist that increases or stabilizes BP during dialysis and may be appropriate for patients who do not oscillate between hypertension and hypotension. Increasing dialysate calcium or using sodium modeling might solve temporary problems with intradialytic hypotension, but the long-term effects on positive calcium and sodium balance likely introduce more harm than benefit if this is used chronically. Finally, relative blood volume monitoring (RBVM) has been proposed as a tool to limit intradialytic hypotension. While this may be useful for assessing ECV and even predicting mortality, its use in a randomized clinical trial was associated with increased mortality and hospitalization. Subsequently, its exact role in prospectively fluid management remains unclear.

A final consideration for patients with intradialytic hypotension is the need to determine if there are potentially reversible abnormalities of cardiac structure and function that are present. Stable patients should be referred for outpatient echocardiography to evaluate for pericardial effusions, systolic dysfunction, or valvular disease. Pericardial effusions should be evaluated by a cardiologist but may ultimately require the dialysis provider to prescribe more intensive dialysis and/or fluid removal. Systolic dysfunction may be related to ischemic cardiomyopathy and may be improved with either revascularization or goal-directed pharmacologic therapy. Valvular disease may be amenable to intervention as well. Diastolic dysfunction may be difficult to manage and may continue to hinder aggressive fluid removal during dialysis.

In summary, intradialytic hypotension frequently complicates HD treatments. While the ideal pre- or postdialysis BP target is yet to be identified from a randomized clinical trial, avoidance of intradialytic hypotension should remain a high priority in the management of HD patients. Avoidance of excessive ultrafiltration rates through limitation of interdialytic weight gain and lengthening treatment time should be considered in patients with intradialytic hypotension. In some patients, this may reflect an inadequate compensatory hemodynamic response to dialysis/ultrafiltration related to cardiac dysfunction or impaired vascular resistance. Targeted treatment should involve a thorough assessment of a patient's cardiac status and underlying comorbidities.

Intradialytic Hypertension

The other side to the U-shaped curve of intradialytic BP change and mortality is the occurrence of intradialytic *hyper*tension. There is no standardized definition of intradialytic hypertension, but it generally refers to increases in BP (systolic or mean arterial) of varying magnitudes from pre- to postdialysis. In fact, there is evidence that regularly

experiencing *any increase* in systolic BP from pre- to postdialysis is associated with higher mortality. The concept of the frequency of intradialytic hypertension is important because almost all dialysis patients will experience intradialytic increases in systolic pressure of at least 10 mm Hg at least intermittently if observed long enough, with one study showing that, on average, patients experienced it in 18% of their treatments over a 6-month period. Patients who experience this in at least one-third of all treatments (on average once a week) are more likely to be reflective of the phenotype associated with poor outcomes.

Compared with the rest of the HD population, patients who experience frequent intradialytic hypertension tend to be older, have lower dry weight, and have evidence of lower nutritional intake based on lower serum albumin and phosphate levels. Despite having lower body weight and body mass index, there is objective evidence that these patients are more volume overloaded. Their dialysis treatments are characterized by increases in vascular resistance during dialysis, and they have higher ambulatory BP between dialysis treatments. The intradialytic increases in vascular resistance have led to speculation that acute release of ET-1 drives the BP up during dialysis, and there is evidence that these patients have more severe chronic underlying endothelial cell dysfunction compared to other dialysis patients.

There have not been any large, randomized trials that conclusively show how to manage patients with intradialytic hypertension using hard clinical outcomes optimally, but studies have at least identified strategies to modify the intradialytic BP trajectory. One randomized crossover trial showed that lowering of dialysate sodium led to BP decreases among patients with recurrent intradialytic hypertension, and another showed that gradual dry weight reduction, in general, induces a more negative intradialytic BP slope. Overall, the presence of intradialytic hypertension should at least alert clinicians to the presence of likely covert ECV overload and identify patients who are at high risk for cardiovascular outcomes in general. Whether the latter is due to the intradialytic hypertension itself or the underlying comorbidities remains unclear.

Blood Pressure Variability

Intradialytic hypotension and intradialytic hypertension are extreme manifestations of the variability in BP that can occur during a single HD treatment. Even in the absence of either of these phenomena, general variability in BP has also been associated with adverse outcomes. BP variability can be defined by the standard deviation of repeated measurements, the coefficient of variation (standard deviation divided by the mean), and metrics considering changes from measurement to measurement. It can be determined from repeated measurements throughout the course of an individual dialysis treatment, from pre- or postdialysis measurements measured repeatedly from treatment to treatment, or even throughout the course of the interdialytic period with ambulatory BP monitoring.

In the ambulatory setting, higher variability of systolic BP (by all definitions) is associated with a higher risk for the composite of mortality, nonfatal myocardial infarction, and stroke. These associations were weakened when considering age, dialysis vintage, underlying cardiovascular disease, and measurements of arterial stiffness with pulse wave velocity. Based on these data, ambulatory BP variability is largely a reflection of impaired vascular health. In the absence of overt intradialytic hypotension, there are little data supporting BP variability as a specific target for therapy modification. Similar poor outcomes have been observed with BP variability occurring during the course of dialysis and, in this context, are also associated with older age and longer dialysis vintage. Intradialytic BP variability is also associated with the amount and rate of fluid removal during the treatment as well.

In summary, BP is constantly changing both during and between dialysis treatments. There is a strong component of this that is related to the amount of rate of ultrafiltration, but there are additional factors related to underlying cardiovascular disease and the patient's physiologic response to dialysis and ultrafiltration. During dialysis, a large amount of BP variability is associated with poor outcomes. Pronounced decreases in BP referred to as intradialytic hypotension, or *any* increase referred to as intradialytic hypertension is particularly indicative of a poor prognosis. The balance between achieving euvolemia without inducing hypoperfusion during the treatment remains a critical challenge in order to limit morbidity and mortality in HD patients.

Treatment Recommendation

Just as there are challenges in defining strict guidelines for BP targets in kidney failure patients, there are also challenges in identifying the ideal therapy. Management will likely require a combination of fluid management as well as pharmacologic antihypertensive therapy.

Fluid Management

The risks of both hypervolemia and overly aggressive fluid removal have been described in detail earlier. A strategy to control BP in HD patients must include consideration of how to prescribe ultrafiltration safely, but patients first need to be educated on the importance of dietary habits that inevitably influence the volume that is removed in a given treatment. Excessive intake of fluid and, more so, dietary sodium hinders the ability to keep the ultrafiltration volume and rate at a minimum. Focusing on sodium restriction not only prevents excessive gains of ECV but also reduces the thirst that drives excessive fluid intake in the first place.

While it may be difficult for many patients to adhere to the recommended restriction to no more than 2 g sodium intake, proper education may provide novel insight and motivation to some patients who were otherwise unaware of the association between sodium intake and weight gain. Additional factors that should be considered are whether uncontrolled hyperglycemia is driving thirst and fluid intake, as well as whether or not patients with residual kidney function are being prescribed diuretics that allow for some fluid removal to take place during the interdialytic period. Once these discussions have been had with patients, the nephrologist must then decide how to proceed with fluid removal during dialysis.

A high predialysis BP is in part a reflection of the recent interdialytic weight gain, while a high post-HD BP or even higher overall ambulatory BP is more strongly associated with chronic ECV overload that may not be obvious through routine clinical assessment. In patients with obvious signs of ECV overload or in patients who have persistent high post-HD BP, a trial of dry weight reduction is warranted. The Dry Weight Reduction in Hypertensive Hemodialysis Patients (DRIP) trial investigated one strategy to achieve BP control through dry weight "probing" over the course of time. In this trial, hypertensive HD patients were randomized to either standard care or intensive ultrafiltration. The latter arm involved reduction in dry weight by 1% each treatment until hypotension or intradialytic symptoms developed. The primary endpoint of mean ambulatory systolic BP was evaluated at 4 weeks and 8 weeks. At the end of the 8-week study, participants randomized to intensive ultrafiltration had reduced dry weight by 1 kg and had reduced the ambulatory systolic BP mean by an additional 7 mm Hg compared to controls. Limitations to the trial include the relatively short duration, the lack of hard clinical outcomes, and the frequency with which intradialytic symptoms occurred in the participants randomized to the intensive arm; however, the study conclusively demonstrated with a rigorous study design the potential benefits of dry weight lowering had on a very important intermediate outcome that is itself associated with mortality.

Subsequent studies have varied in the specific fluid removal approaches but preserve the focus of gradual dry weight lowering to improve BP. Advances in technology to assess for ECV overload (beyond hypertension itself) have provided investigators with additional tools to determine how, aggressively, to remove fluid from treatment to treatment. In one study, patients were randomized to standard care or gradual fluid reduction based on the persistence of "lung comets" or pockets of pulmonary fluid identified with lung ultrasonography. In the intervention group, additional fluid was removed in increments of 0.1–0.2 L per treatment. This approach was less aggressive than in the DRIP trial, but the intervention group still experienced greater reduction in dry weight and a greater reduction in ambulatory BP. Importantly, there was no difference between groups in the frequency of intradialytic hypotension. An additional benefit from the intervention was improvement in the secondary outcome of left ventricular filling pressure that was also seen in the intervention group. Another small study compared standard care to volume management guided by objective evidence of ECV overload assessed by bioimpedance spectroscopy. Again, the increments of additional fluid removal per treatment were fairly small, 0.2 L per treatment. Ambulatory BP was not assessed in this trial, but the intervention group had significant reductions in predialysis systolic BP, pulse wave velocity, as well as lower mortality. The lack of difference between groups in intradialytic hypotension or cramps again emphasizes that dry weight can be lowered safely if done gradually.

While the majority of HD patients receive thrice-weekly in-center HD, there are lessons to be learned from the observations that have been made in patients who receive alternative schedules of HD. Randomized trials have shown that patients prescribed short daily HD experience significant reductions in pre- and post-HD systolic and diastolic BP, while nocturnal dialysis prescriptions resulted in significant improvement in predialysis systolic BP with trends toward improvement in other peridialytic parameters. The potential to improve both ECV and phosphate control stands out as logical mechanisms through which these benefits are derived, but currently, the effects of these dialysis prescriptions on ambulatory BP are not well known.

As mentioned earlier in the section on intradialytic hypotension, the role of dialysate sodium restriction remains controversial. One has to consider the risk of inducing BP decreases from low dialysate sodium with the risk of diffusing additional sodium (and thus provoking thirst and interdialytic weight gains) with higher dialysate sodium concentrations. The observational data on dialysate sodium and gradients can be conflicting and confounded by underlying comorbidities that are associated with varying serum sodium levels, and there are insufficient data from prospective clinical trials to conclusively guide the decision of how to prescribe dialysate sodium specifically to achieve any particular outcome.

Pharmacologic Antihypertensive Use

In situations where dry weight challenges are no longer possible due to patient symptoms (whether the patient is truly at "dry weight or not") or nonadherence to either fluid intake or dialysis time, one or more antihypertensive drugs are usually necessary. There is evidence from two separate meta-analysis studies that show that the use of antihypertensive drugs is associated with a reduction in both cardiovascular events and mortality in hypertensive HD patients. Just as in patients without kidney failure, it is important also to consider factors related to the likelihood that one will adhere to the regimen (number of doses per day, side effects) as

well as any possible advantages or disadvantages of the timing of the doses. Once-daily medications are preferable to minimize missed doses, and taking the medication at night might offer theoretical benefits, such as restoring the natural nocturnal "dipping" pattern of BP and limiting the risk of intradialytic hypotension compared to morning or daytime doses. The primary question that remains is which agents or class of agents is preferred, although patients may ultimately require multiple classes of drugs. The focus of this section is on what is known about the more commonly prescribed antihypertensive drugs with an emphasis on available data in the HD population. The reader should seek more extensive pharmacologic literature for guidance on prescribing in the context of other medications and comorbidities. Table 44.3 includes information on the dialyzability, kidney clearance, dose range in normal kidney function, and recommended starting dose for HD patients for many of the commonly prescribed antihypertensive drugs.

Inhibitors of the Renin-Angiotensin System

Because of the beneficial effect of inhibitors of the renin-angiotensin-aldosterone system (RAAS) in CKD, there is interest in how these agents can be used in kidney failure patients. There is currently conflicting evidence regarding the benefits of RAAS inhibitors in dialysis patients. Observational research had suggested a lower mortality with angiotensin-converting enzyme (ACE) inhibitors, but this was not seen in a randomized trial comparing fosinopril to a placebo. The benefits of angiotensin receptor blocker (ARB) have also not been consistently shown, with the larger randomized trial failing to show any mortality benefit. However, RAS inhibitors continue to be frequently prescribed, with meta-analysis data showing a benefit with at least the intermediate outcome of left ventricular hypertrophy regression.

Although these drug classes target the same system, one major difference between ACE inhibitors and ARB is their dialyzability. Other than fosinopril, most other ACE inhibitors are more readily cleared by dialysis, with enalapril and lisinopril having the highest dialyzability. In comparison, most ARBs are not removed by the dialysis procedure. Therefore, it may be appropriate to consider a change from ACE inhibitor to ARB (or at least to fosinopril) to optimize the long-term antihypertensive effect.

Mineralocorticoid receptor antagonists (MRAs) such as spironolactone or eplerenone are recommended as therapy for patients without kidney failure and resistant hypertension defined as inadequate BP control despite three maximally dosed agents (including a diuretic). The risk of hyperkalemia with these agents is significantly increased in the context of use of another RAS inhibiting drug as well as decreased glomerular filtration rate. Some of this risk may be offset by limited effect on kidney potassium clearance in patients who are already anuric, as well as the ability to remove potassium regularly with scheduled dialysis. Prospective studies of MRA in HD patients have carefully excluded patients who are prone to hyperkalemia but have, in general, found there to be manageable increases in serum potassium. Potential benefits include regression of left ventricular hypertrophy as well as the extrapolated benefits of improvement in systolic heart function among nondialysis patients with heart failure. There are ongoing clinical trials further evaluating the benefits in HD. Frequent monitoring of potassium must be undertaken of HD patients receiving MRA, and it should not be used in patients who are hyperkalemic at baseline.

Adrenergic Receptor Antagonists

While beta-adrenergic receptor antagonists are not considered first-line agents in essential hypertension or even CKD, there is emerging evidence of benefits offered to patients on HD. For patients who have known systolic heart failure, carvedilol has been shown in a randomized trial to improve survival compared to placebo when added to other goal-directed therapies. In one randomized trial comparing thrice-weekly atenolol to lisinopril in HD patients with left ventricular hypertrophy, cardiovascular events and hospitalizations were found to be more common in the lisinopril group. Epidemiologic studies have attempted to identify which beta-blockers might offer the most benefit in HD patients. In one study, carvedilol use was found to be associated with higher 1-year mortality compared to metoprolol. In this observational study of two drugs, it is not possible to address whether factors related to dialyzability or adrenergic receptor specificity played any role in the outcome difference. Another cohort study reported that highly dialyzable beta-blockers were associated with a higher mortality risk than low-dialyzability beta-blockers. Among the commonly prescribed beta-blockers (including those with additional alpha-adrenergic receptor antagonism), metoprolol and atenolol have the highest dialyzability, while labetalol, carvedilol, and propranolol have limited clearance with dialysis.

Drugs that exclusive block the alpha-adrenergic receptor (doxazosin, prazosin, terazosin) may be effective add-on therapies to other antihypertensive drugs and can even be used in patients who are already receiving beta-adrenergic receptor blockers with some alpha blockade as well (carvedilol, labetalol). The tendency for exacerbating orthostatic hypotension makes these drugs better suited for use before bedtime. They may also be appropriate for male patients with problematic prostatic hypertrophy.

Calcium Channel Blockers

Calcium channel blockers are frequently prescribed in the general population and thus frequently continued or

TABLE 44.3 Dialyzability, Normal Dosing, and Dialysis Dosing of Commonly Prescribed Antihypertensive Drugs

	Dialyzable	Usual Dose for Normal Kidney Function	Starting Dose in Hemodialysis
Angiotensin Converting Enzyme Inhibitors			
Benazepril	No	10–40 mg daily	5 mg daily
Captopril	Yes	12.5–50 mg three times a day	12.5 mg three times a day
Enalapril	Yes	5–40 mg daily	2.5 mg daily after dialysis-on-dialysis days
Fosinopril	No	10–40 mg daily	10 mg daily
Lisinopril	Yes	10–40 mg daily	2.5 mg daily
Ramipril	Yes	2.5–20 mg daily	2.5 mg three times weekly (dosed after dialysis)
Angiotensin Receptor Blockers			
Candesartan	No	8–32 mg daily	4-8 mg daily
Irbesartan	No	150–300 mg daily	75 mg daily
Losartan	No	50–100 mg daily	25 mg daily
Olmesartan	No	20–40 mg daily	5 mg daily
Telmisartan	No	20–80 mg daily	20 mg daily
Valsartan	No	40–320 mg daily	40 mg daily
Mineralocorticoid Receptor Antagonists			
Spironolactone	No	25–100 mg daily	12.5 mg daily or every other day (based on recommendations for severely impaired GFR)
Eplerenone	No	50–100 mg daily	No recommended dose (per labeling is contraindicated in advanced renal failure)
Beta-Adrenergic Receptor Antagonists (Including Those with Combined Alpha and Beta Antagonism)			
Atenolol	Yes	25–100 mg daily	25 mg after each dialysis treatment
Bisoprolol	Yes	2.5–10 mg daily	2.5 mg daily
Carvedilol	No	12.50 mg daily	6.25 mg twice daily
Labetalol	No	200–800 mg daily	100 mg twice daily
Metoprolol	No	100–200 mg daily	50 mg twice daily
Propranolol	No	80–160 mg daily	40 mg twice daily
Alpha-adrenergic Receptor Antagonists			
Doxazosin	No	1–16 mg daily	1 mg daily
Prazosin	No	2–20 mg daily	1 mg twice daily
Terazosin	No	1–20 mg daily	1 mg daily
Calcium Channel Blockers			
Amlodipine	No	2.5–10 mg daily	2.5 mg daily
Diltiazem (long acting)	No	120–360 mg daily	120 mg daily
Felodipine	No	2.5–10 mg daily	2.5 mg daily
Nifedipine (extended release)	No	30–90 mg daily	30 mg daily
Other Commonly Prescribed Antihypertensive Drugs			
Clonidine	No	0.1–0.8 mg daily (in divided doses)	0.1 mg twice daily or 0.1 mg/day for transdermal patch
Guanfacine	No	1–3 mg daily	1 mg daily
Hydralazine	Yes	100–200 mg daily	10 mg three to four times daily titrated up to 25mg four times daily after several days
Minoxidil	No	5–100 mg daily	5 mg daily

GFR, Glomerular filtration rate.

started as additional therapy in patients on HD as well. There is evidence from a randomized trial that addition of the long-acting dihydropyridine calcium channel blocker amlodipine resulted in less frequent occurrence of the composite of mortality and nonfatal cardiovascular events in comparison to the placebo, although there was no difference in mortality alone. Amlodipine and other long-acting dihydropyridines might be appropriate choices for patients who have chronic stable angina despite beta-blocker therapy, although one should monitor for the side effects of peripheral edema or even pulmonary edema. They have limited clearance with dialysis, and they do not require specific dose adjustments in HD patients. Of note, the short-acting form dihydropyridine calcium channel blocker nifedipine should be avoided for the acute management of severe hypertension because of the risk for adverse acute cardiovascular events. Nondihydropyridine calcium channel blockers such as diltiazem and verapamil can be considered but should be avoided if beta-blockers are being concurrently used as well as in patients with severe heart failure.

Other Frequently Prescribed Antihypertensives

Hydralazine is a short-acting vasodilator that is commonly prescribed for both acute hypertension and add-on therapy for patients with chronic hypertension that is refractory to multiple other agents. There are no specific studies evaluating the benefits of hydralazine in HD patients, but the need to dose it several times a day may make adherence difficult. The short half-life makes it ideal to hold prior to dialysis, particularly in patients prone to intradialytic hypotension. The potential adverse effect of a lupus-like syndrome should be monitored when hydralazine is prescribed.

Clonidine is a centrally acting adrenergic receptor blocker that is not a first-line antihypertensive but is a frequently utilized drug for patients with resistant hypertension regardless of kidney function. Clonidine is often available in outpatient dialysis clinics for patients with severe asymptomatic hypertension as predialysis or intradialytic therapy. One of the major concerns of clonidine therapy is the potential for rebound hypertension when taken sporadically. A transdermal option is available that might limit this rebound but still requires regular changing of the patch on a weekly basis. An alternative option is guanfacine, another centrally acting antihypertensive, which has a longer half-life and thus lowers risk of rebound hypertension if taken only once daily (or nightly). Both of these agents have numerous side effects and are typically prescribed only to patients who are inadequately responding to multiple other agents and presumably appropriate management of ECV. Intradialytic clonidine should be avoided in patients whose BP would otherwise respond favorably to fluid removal and who might experience severe episodes of intradialytic hypotension with additional drug therapy.

Minoxidil is a potent antihypertensive drug that is also typically reserved for patients who remain hypertensive despite multiple other medications. Due to associations with pericardial effusions, particularly in patients with ECV overload, attempts to optimize ECV should be implemented in addition to regular cardiac physical exams to assess for pericardial rubs. The common side effect of promoting hair growth should be explained to patients before starting treatment as well.

Conclusion

In conclusion, hypertension is extremely common in HD patients. The etiology is multifactorial, with a substantial contribution from ECV overload, along with excessive RAS activity, sympathetic nervous system activity, endothelial cell dysfunction, among others. The significance of individual BP measurements in the dialysis unit is not clear, but higher overall BP burden assessed with multiple measurements, particularly during the interdialytic period, is associated with higher morbidity and mortality. Major obstacles in the management of hypertension include the frequent changes that occur in BP during and between dialysis, which themselves are associated with a worse prognosis. There is no clear guidance on the ideal BP target for HD patients. Control of ECV is critical to lowering BP, but intradialytic hypotension and rapid ultrafiltration rates should be avoided. Slow, persistent attempts to control dry weight, along with adherence to a low-sodium diet, may help achieve euvolemia more safely. As the alternative forms of dialysis prescriptions become more widely implemented (i.e., short daily dialysis, nocturnal dialysis), we should learn more about the long-term benefits that these offer regarding BP control and overall cardiovascular morbidity and mortality.

Table 44.4 provides some recommendations to consider for comprehensive evaluation and management of hypertensive HD patients. In most patients, pharmacologic antihypertensives will be required. While lowering BP with medications is associated with improved outcomes, there is no class of antihypertensive drug that is clearly superior to others with regard to mortality. There is conflicting data on the effects of mortality with RAS inhibiting drugs, but these agents may have benefits on intermediate outcomes related to cardiac structure and function. Beta-blockers are frequently prescribed agents, and further prospective studies are required to establish their superiority to other classes (including RAS inhibitors) as well as determine specific benefits related to dialyzability and/or cardioselectivity. Numerous other agents can be considered, with appropriate attention to known side effects. Despite the widespread prevalence of hypertension among dialysis patients, the optimal management approach requires consideration of specific factors relevant to each individual patient.

TABLE 44.4 Summary of the Approach to the Evaluation and Management of Hypertensive Hemodialysis Patients

1. Assess for hypertension ideally using multiple interdialytic measurements if available, including ambulatory blood pressure monitoring.
   a. If interdialytic blood pressure measurements are not available, calculate mean intradialytic (including predialysis and postdialysis measurements) as opposed to limiting assessment to just pre or post dialysis measurements
2. Evaluate for overt signs of volume overload (peripheral edema, jugular venous distention).
   a. Provide education on dietary sodium restriction (2 g daily) and fluid restriction.
   b. Slowly challenge dry weight over multiple dialysis treatments by as little as 0.2 kg per treatment if tolerated.
      i. Avoid intradialytic hypotension, specifically nadir systolic blood pressure < 90 mm Hg or < 100 mm Hg if predialysis systolic blood pressure is greater than 160 mm Hg. If present and the patient has persistent interdialytic and/or peridialytic hypertension, consider
         1. Lengthening dialysis time per treatment. Ultrafiltration rates > 13 mL/kg/h should be avoided, but the ideal rate may in fact be much lower than this
         2. Offering additional ultrafiltration treatments
         3. Prescribing diuretics to patients with residual renal function
         4. Evaluation of cardiac structure with echocardiogram to evaluate for pericardial effusion, valvular disease, or systolic dysfunction that might require intervention by cardiologist.
         5. Working with primary care physician or endocrinologist to optimize glycemic control if there is persistent hyperglycemia
         6. Avoid dosing of antihypertensives shortly before dialysis. Consider nighttime dosing for once daily medications or holding morning doses for medications given several times a day
         7. Avoid eating during dialysis treatment
   c. If intradialytic *hyper*tension is present, continue to suspect persistent covert extracellular volume overload.
   d. If large interdialytic weight gain persists, and intradialytic hypotension is NOT present
      i. Consider lowering of dialysate sodium
      ii. Reeducate on dietary sodium restriction, fluid restriction
      iii. As previously, consider diuretics and optimization of glycemic control.
   e. Continue to assess interdialytic blood pressure burden.
3. Optimize pharmacologic antihypertensive regimen (can occur simultaneously with #2 if BP control is needed more urgently). There is no clear-cut superior class of drugs with regard to mortality risk.
   a. Consider prescribing once daily medications to optimize adherence.
   b. ACE inhibitors/angiotensin receptor blockers
   c. Beta-blockers
   d. Long-acting dihyropyridine calcium channel blockers
   e. Additional agents if necessary including
      i. Alpha adrenergic receptor blockers
      ii. Hydralazine
      iii. Minoxidil
      iv. Clonidine (preferably transdermal)/guanfacine

ACE, Angiotensin-converting enzyme; *BP*, blood pressure.

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45

Arrhythmias in Hemodialysis Patients

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Cardiac rhythm disturbances are common in dialysis. Multiple studies have shown a high prevalence of ventricular and atrial ectopy and conduction abnormalities in hemodialysis patients, reflecting both the proarrhythmic nature of the hemodialysis process itself and the high burden of structural heart disease in kidney failure populations. The prevalence of chronic or recurrent rhythm disturbances, especially atrial fibrillation, is several-fold higher than in the general population. Treatment of arrhythmias in dialysis patients can be challenging, and in many instances, the risk-to-benefit ratio of many therapies is altered or uncertain.

The present chapter summarizes what is known about the etiology and management of rhythm disturbances in hemodialysis. The major emphasis is on chronic management of arrhythmias in dialyzed patients, especially atrial fibrillation. Because the acute management of life-threatening unstable arrhythmias deviates little from current advanced cardiac life support (ACLS) guidelines, only important differences are highlighted. The reader is encouraged to review the latest ACLS guidelines (see Recommended Reading).

It should be remembered that most of the recommendations in this chapter are based on imperfect or evolving data, mostly in patients without kidney failure. In the future, direct evidence in hemodialysis populations may help refine the arguments presented here.

Etiology and Prognosis

Both patient factors and dialysis factors contribute to arrhythmic risk. Significant underlying cardiac disease, present in the majority of hemodialysis patients, is independently associated with conduction disturbances, atrial and ventricular ectopy, and death. Superimposed on this substrate, changes in volume and extracellular ion composition during dialysis enhance myocardial irritability (Table 45.1). Ventricular ectopy and atrial ectopy are more frequent during dialysis than in the interdialytic period. Both atrial (p-wave) and ventricular (t-wave) dispersions increase during dialysis, enhancing the likelihood of reentrant arrhythmias. Rapid extracellular fluid (ECF) volume fluxes are being associated with catecholamine surges and subendocardial ischemia, which are, in turn, associated with ventricular ectopy. Rapid lowering of potassium, particularly in patients taking cardiac glycosides, is arrhythmogenic, and attenuation of these changes by stepwise ramping of dialysate potassium during dialysis seems to reduce ventricular ectopy. Many of the cardiac drugs commonly used in hemodialysis patients (e.g., digitalis preparations) exhibit arrhythmogenic toxicities because of altered pharmacokinetics, end-organ effects, or both.

The prognostic impact of arrhythmias in hemodialysis patients is incompletely defined. Frequent or complex ventricular ectopy is associated with lower survival, but this effect is not independent of age, hypertension, and underlying heart disease and may simply be a marker of poor cardiac status.

Management

General Considerations

Unstable Rhythms

Acute unstable or life-threatening rhythms, defined as heart rhythms associated with chest pain or evidence of circulatory insufficiency (e.g., frank shock, hypotension, impaired mentation), should be managed as per current ACLS guidelines. As a general rule, the dialysis procedure should be stopped unless a clear metabolic precipitant correctable by dialysis is present (e.g., hyperkalemia induced heart block). Intravenous access via the fistula or central line should be maintained. Because a thorough discussion of ACLS procedures is beyond the scope of this chapter, the reader is encouraged to download the latest edition of the ACLS recommendations (see Recommended Reading). Any additional considerations in hemodialysis patients are discussed under specific rhythm disturbances.

Avoiding Arrhythmogenic Triggers

Avoidance of arrhythmogenic stimuli during dialysis may be helpful, particularly in patients in whom dialysis reliably precipitates arrhythmias. Measures such as strict control of interdialytic fluid gain and potassium intake may decrease

TABLE 45.1 Factors That May Precipitate Arrhythmias During Hemodialysis

Digitalis
Acute volume shifts
Hypokalemia
Hypocalcemia
Hypomagnesaemia
Myocardial ischemia

the need for aggressive ultrafiltration and low potassium dialysate. Substitution of normal instead of the usually elevated calcium bath may be helpful. Discontinuation of arrhythmogenic drugs (e.g., cardiac glycosides) should be seriously considered. Conversion to an alternative dialysis modality, such as peritoneal dialysis, short daily hemodialysis, or long hours of nocturnal hemodialysis, can be tried if other measures fail.

Treatment of Underlying Cardiac Disease

Aggressive medical and surgical therapy of underlying cardiac disease has been shown to prolong life and decrease morbidity in the general population. In contrast, with few exceptions, specific antiarrhythmic therapy does not prolong life and may increase mortality in patients with heart disease. In hemodialysis patients with arrhythmias, a search for an aggressive treatment of ischemic heart disease and left ventricular dysfunction is probably more important than antiarrhythmic therapy. Appropriate indications for established life-saving therapies such as aspirin, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and coronary revascularization are discussed elsewhere.

Specific Rhythm Disturbances

Ventricular Ectopy

Ventricular ectopic beats (also called ventricular premature contractions) are a common rhythm disturbance in dialysis. They may be precipitated or exacerbated by acute changes in volume and ECF composition. Minimizing these alterations may reduce or eliminate the ectopy (Table 45.1). Medications should be reviewed to identify and stop proarrhythmia medications (e.g., domperidone). Blood chemistry should be reviewed to identify and correct derangements in calcium, potassium, and magnesium.

Complex ventricular ectopy is usually associated with underlying structural heart disease. Underlying cardiac disease should be aggressively sought and treated. With a cardiac history, electrocardiogram (ECG), echocardiogram, and cardiac perfusion scan are reasonable investigations to request in this regard. Referral to cardiology is indicated if significant cardiac disease is identified since treatment (e.g., coronary revascularization) will typically improve symptoms. In addition, cardiology referral is also indicated in patients with persistent ectopy despite review and optimization of dialysis prescription and medications, or if ectopy is complex or associated with persistent symptoms. Further therapeutic options for symptomatic patients or patients with frequent ectopic rhythms may include catheter ablation of an ectopic focus and consideration of implantable cardioverter defibrillator (ICD) in patients meeting ICD criteria.

Ventricular Tachycardia

A wide QRS complex characterizes ventricular tachycardia. The complexes may be identical (monomorphic) or variable (polymorphic). Polymorphic ventricular tachycardia often oscillates between high and low amplitude as if the electrical axis were twisting (Torsades de pointes).

Although a wide complex rhythm can be supraventricular (SVT) in origin, it is ventricular in more than 90% of patients who are older than 65 or who have known structural heart disease. ECG-based criteria have been developed to help distinguish SVT from ventricular rhythms, but they are cumbersome to use and have poor predictive values for SVT tachycardia given the low pretest probability of SVT in such patients. Wide complex tachycardia in dialysis patients should be treated as ventricular tachycardia unless the patient has known recurrent SVT tachycardia with aberrancy.

Acute management of monomorphic and polymorphic ventricular tachycardia is the same for dialysis patients as it is for nondialysis patients. These approaches are well summarized in the current ACLS guidelines and will not be elaborated here as they require no modification. Polymorphic ventricular tachycardia may be the result of hypomagnesemia, which should be corrected, or medications that prolong QT (e.g., quinine, domperidone, metoclopramide, proton pump inhibitors, certain antidepressants, or antiarrhythmic drugs [e.g., sotalol, amiodarone]), which should be discontinued. Long-term management will depend on the underlying cause (e.g., coronary heart disease, cardiomyopathy), and some patients may require ICD implantation if indicated.

Paroxysmal Supraventricular Tachycardia

Paroxysmal SVT tachycardia is usually due to an atrioventricular (AV) nodal reentrant circuit and rarely to an auxiliary AV bypass tract (Wolff-Parkinson-White [WPW] syndrome). Synchronized electrical cardioversion is the treatment of choice for patients with evidence of hemodynamic instability (e.g., systolic blood pressure < 90 mm Hg, congestive heart failure, chest pain, or altered mental status). Termination of stable paroxysmal SVT tachycardia can be done with vagal maneuvers (carotid sinus massage) or the use of AV nodal blocking agents, such as adenosine, diltiazem, or metoprolol, as described in the ACLS guidelines. Chronic therapy is rarely necessary for paroxysmal SVT tachycardia. In patients with recurrent symptomatic

paroxysmal SVT tachycardia or WPW, catheter ablation of the reentrant pathway is the therapy of choice.

Atrial Fibrillation

Atrial fibrillation is the most common chronic arrhythmia in dialysis patients, having a prevalence of about 12% (range 3% to 34%) and an incidence of about three events (range one to six) per 100 patient-years. These rates are about double the rates reported for older adults (age > 55) in the U.S. general population.

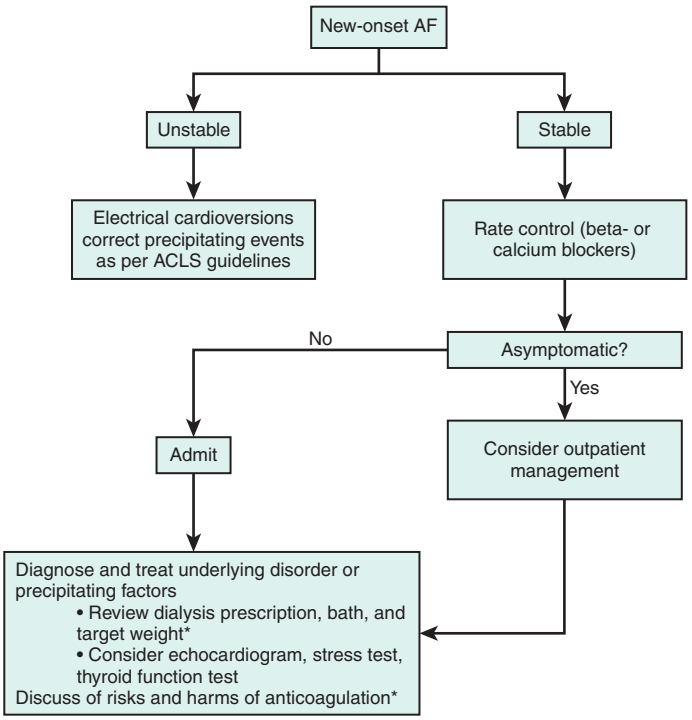
Atrial fibrillation may be chronic (i.e., always present), persistent, or paroxysmal. Persistent atrial fibrillation is defined as atrial fibrillation that persists for greater than 7 days or has required cardioversion for termination of the rhythm. Paroxysmal atrial fibrillation is self-terminating, usually within 24–48 hours, and is often recurrent. Valvular atrial fibrillation refers to atrial fibrillation occurring in the setting of valvular heart disease (e.g., rheumatic mitral valve disease) and has a much higher embolic risk than nonvalvular atrial fibrillation.

The significance of atrial fibrillation is twofold. First, it is a marker of probable underlying structural heart disease, which should be investigated and treated. Second, it may be associated with a significantly higher risk of embolic stroke in dialysis patients. This second point, and its corollary, whether anticoagulation with warfarin should be prescribed to all dialysis patients with nonvalvular atrial fibrillation, is the subject of significant current debate and uncertainty, as will be discussed in detail later.

Approach to New-Onset Atrial Fibrillation in the Dialysis Unit

New onset of atrial fibrillation during the dialysis procedure is not a rare event in the dialysis unit. Some patients will have significant symptoms (chest pain, heart failure) or hemodynamic instability and will require immediate transfer to a monitored setting (e.g., emergency department, coronary care unit) for management by a cardiologist. However, many patients will remain asymptomatic. In these cases, the diagnosis is typically made when the nurse notes a fast irregular pulse and an ECG is ordered that confirms atrial fibrillation. In our opinion, such stable cases can be managed in an outpatient setting (Fig. 45.1), provided that a low clinical probability of acute coronary syndrome, heart failure, pulmonary thromboembolism, or sepsis can be established.

Our approach, therefore, is to obtain a focused cardiovascular history and physical, an ECG, cardiac enzymes, a chest x-ray, a complete blood count (CBC), and a transcutaneous O_2 saturation before the dialysis treatment is over. If the clinical suspicion of acute coronary syndrome, pulmonary thromboembolism, or sepsis is low, if the previous ancillary tests are negative or normal, if the ventricular rate is less than 150, and if the patient is otherwise relatively high functioning, then outpatient management is selected. An oral rate control agent is prescribed, and the first dose is given in the unit (see section on rate control). We typically defer the decision to anticoagulate (see section on anticoagulation) pending a more thorough risk-benefit discussion



• **Fig. 45.1** Overview of the treatment of acute atrial fibrillation *(AF)* in hemodialysis patients. *ACLS*, Advanced cardiac life support.

in follow-up. The dialysis bath, ultrafiltration profile, and patient dry weight are reviewed and altered if possible to make them less arrhythmogenic (see general considerations above). The patient is then sent home at the end of the treatment with instructions to return to the emergency room if symptoms or problems arise.

The rate of spontaneous termination of acute atrial fibrillation in nondialysis settings is high: 30% at 3 hours, 60% by 24 hours, and close to 80% by 48 hours. Although data are not available for dialysis, we have observed that many patients will spontaneously convert to sinus rhythm by the time they present for their next dialysis treatment. In most cases, the rate control agent may be discontinued if there is spontaneous conversion to sinus rhythm. At this time, an echocardiogram and an imaging cardiac stress test (e.g., adenosine sestamibi perfusion study) are requested to look for treatable structural heart disease, and thyroid function is assessed to exclude hypothyroidism. Finally, a careful weighing of the benefits and harms of anticoagulation for stroke prevention as described later is undertaken.

The reader is reminded that this approach is based on opinion and clinical experience at our center and not on evidence from randomized controlled trials (RCTs).

Rate Control

Calcium blockers and beta-blockers are good first-line agents for rate control in most patients. Beta-blockers should be avoided in patients with reactive airway disease. Although digoxin is effective at rest, it is less effective than either beta or calcium blockers in controlling heart rate during exercise. Moreover, toxicity can be a problem in dialysis patients. For these reasons, it is considered a second-line agent. Most guidelines recommend titration of the rate control agent to achieve a resting heart rate of 80–90 beats/min. Chronic heart rates above 130 beats/min have been associated with cardiomyopathy.

The approach to rate control of paroxysmal atrial fibrillation is similar, although control of the rate during paroxysms may be more difficult. People with very rare paroxysms, who tolerate a fast ventricular response well, can probably forego chronic AV nodal-blocking drugs. Digoxin is poorly efficacious in paroxysmal atrial fibrillation and is not recommended. Beta-blockers and nondihydropyridine calcium blockers can successfully control ventricular rates during paroxysmal atrial fibrillation.

Stroke Prevention

Nonvalvular Atrial Fibrillation

In contrast with the general population, there is strong, concordant RCT evidence that anticoagulation with warfarin is superior to antiplatelet therapy for the prevention of stroke and all-cause death in patients with nonvalvular atrial fibrillation; the evidence is much less clear in dialysis patients (extensively reviewed in Clase et al. (2012)). Although the risk of stroke is higher, the risk of bleeding is also much higher, especially for catastrophic bleeding, for example, intracranial hemorrhage risk is 2.6% per year in dialysis patients on warfarin vs 0.4% per year in nondialysis cohorts. This higher risk of catastrophic bleeding may nullify any net clinical benefit of anticoagulation. The efficacy of warfarin may also be lower in dialysis patients, further diminishing the benefit-to-risk ratio of treatment. Several recent, large observational studies have noted a disturbing trend toward net harm in dialysis patients with atrial fibrillation treated with warfarin (reviewed in Clase et al. (2012)). In the absence of direct RCT evidence in dialysis patients, it is unknown whether warfarin reduces the risk of stroke or death in dialysis patients with atrial fibrillation. This uncertainty is reflected in highly variable practice patterns worldwide. For example, fewer than 3% of dialysis patients with atrial fibrillation are anticoagulated with warfarin in Germany, compared with 30%–40% of atrial fibrillation patients on dialysis in the United States and Canada.

Faced with the current clinical uncertainties, we believe that the dialysis practitioner has three possible, equally valid, options: (1) no anticoagulation, (2) anticoagulation as per recommendations in the general population ($CHA_2DS_2VASc > 1$, absent contraindication to warfarin), or (3) individualized care based on individual patient risks and preference. Of these options, we prefer the third (individualization). First, we formally calculate the CHA_2DS_2VASc (stroke risk) and HAS-BLED (bleeding risk) scores to see if either clotting (CHA_2DS_2VASc) or bleeding (HAS-BLED) risk is dominant. If one risk dominates, the decision is made simple; no anticoagulation if bleeding is clearly the dominant risk versus proceed with anticoagulation if stroke risk dominates. In most cases, however, both scores will be moderate or high, in which case we heavily weigh patient preference. Most patients are much more stroke-averse than bleed-averse, and unless there is a huge, estimated risk of bleeding, most will elect a trial of anticoagulation. Conversely, if the consensus of patient and team is not to anticoagulate, we typically recommend continuing or starting antiplatelet therapy with aspirin.

Valvular Atrial Fibrillation

The risk of embolic stroke from valvular atrial fibrillation is much higher than from nonvalvular atrial fibrillation. There is far less uncertainty on this question, and anticoagulation is probably reasonable for all dialysis patients with valvular heart disease (especially mitral).

Warfarin Versus Non–Vitamin K Antagonist/Direct Oral Anticoagulants

Several new direct thrombin inhibitors have been approved for anticoagulation in atrial fibrillation. The main advantages of these new agents over warfarin are a fixed-dose administration and absent need for international normalized ratio (INR) monitoring. The major disadvantages are the long half-life and lack of reversibility in cases of bleeding or overdose. Of these agents, all except apixaban are contraindicated in kidney failure. The approval by the Food

and Drug Administration (FDA) for apixaban use in kidney failure was based solely on pharmacokinetic data and not on efficacy and safety data in this population. In the absence of such data, the concerns described earlier regarding warfarin therapy in dialysis patients also apply to apixaban.

Implications for Future Research

We believe that the question of whether we should or should not anticoagulate dialysis patients with nonvalvular atrial fibrillation, and the related question of whether non–vitamin K antagonist (NOAC)/direct oral anticoagulants (DOACs) are superior to warfarin for this purpose are critical knowledge gaps that urgently need to be addressed with RCTs. Fortunately, such trials are ongoing (SAFE-D, https://clinicaltrials.gov/ct2/show/NCT03987711; RENAL-AF, https://clinicaltrials.gov/ct2/show/NCT02942407; and AXADIA, https://clinicaltrials.gov/ct2/show/NCT02933697).

Rhythm Control Versus Rate Control

Physicians have debated for years whether attempts should be made to achieve and maintain sinus rhythm, using drugs, cardioversion, catheter ablation, or various combinations of these, in nonvalvular atrial fibrillation. A recent meta-analysis of seven RCTs concluded that rate control and rhythm control are equivalent in terms of major clinical outcomes (all-cause death, cardiovascular death, and stroke). There was insufficient evidence to conclude whether catheter ablation was better than pharmacological interventions. Thus, given equivalent efficacy, we generally recommend a rate control approach because it is simpler and is associated with lower health care costs, and there is less concern about the risks of antiarrhythmic drug therapy (such as torsade de pointes) or invasive procedure (radiofrequency catheter ablation).

Rhythm control strategies should be considered in individuals who remain symptomatic despite rate control (e.g., difficult to control rate, frequent heart failure episodes, frequent symptomatic palpitations). Given the added complexity and different risks of a rhythm control approach, we recommend such strategies by prescribed and supervised by a cardiologist.

Bradyarrhythmias

Bradycardia is defined as a heart rate less than 60 beats/min. Immediate treatment is indicated for cardiovascular instability (hypotension systolic blood pressure <90, congestive heart failure, acute myocardial infarction, or chest pain). Early transthoracic pacing, if available, is preferable to repeated doses of atropine. Reversible causes of bradycardia, such as sinoatrial or AV node depression with drugs (digoxin, calcium blockers, beta-blockers), should be sought. Hyperkalemia may manifest as sinoatrial arrest or AV block with a junctional or ventricular escape rhythm in the absence of classical QRST changes. Temporization with intravenous calcium gluconate and insulin/glucose is useful until the patient is dialyzed. Many patients on dialysis may have chronic sinoatrial or AV nodal disease secondary to age, coronary artery disease, or calcification of the AV valve annuli. In these cases, a permanent pacemaker is required if a superimposed reversible cause is not identified or if there is either third-degree or type 2 second-degree AV block. Finally, ventricular ectopy in the form of ventricular bigeminy (a normal beat followed closely by a ventricular ectopic beat) can mimic a bradyarrhythmia. In bigeminy, the ectopic beat occurs so closely after the normal beat that the ventricle has no chance to fill, and so there is no ejection of significant blood volume into the circulation. The ectopic beat prolongs the refractory period, prolonging the time until the next perfused beat. ECG will show that the electrical rate is exactly twice the (slow) pulse rate, with each normal QRS closely coupled to an ectopic beat. This phenomenon is often well tolerated and asymptomatic and usually responds to the measures described in the section on ventricular ectopy.

Cardiac Arrest in the Dialysis Unit

Cardiac arrest during a dialysis run is, fortunately, a rare event, occurring between three and four times per 100,000 treatments. The usual rhythms associated with a pulseless state are ventricular fibrillation, ventricular tachycardia, asystole, and pulseless electrical activity (PEA). The ACLS guidelines for management of these rhythms are published elsewhere and require little modification. Only special considerations in dialysis patients are discussed here.

Asystole in the general adult population is most often an agonal rhythm. However, asystolic arrest in a hemodialysis patient may reflect profound bradyarrhythmia secondary to hyperkalemia. As discussed earlier, this phenomenon may occur in the absence of an antecedent, classical QRST changes, particularly in patients with underlying sinoatrial and AV conduction problems who may not exhibit a junctional or ventricular escape rhythm. It should be suspected in patients arresting with asystole immediately prior to dialysis. Treatment with calcium gluconate and insulin/glucose may be lifesaving.

Cardiac tamponade in patients with uremic pericarditis is a correctable cause of PEA in hemodialysis patients. Immediate volume infusion to improve cardiac filling and pericardiocentesis to decompress the pericardial sac are necessary for survival.

The long-term prognosis of witnessed cardiac arrest in the hemodialysis unit is abysmal. Only 15%–19% survive to 30 days, and only 7%–9% make it to 1 year after the event.

Sudden Cardiac Death

Sudden cardiac death (SCD) is defined as death from an unexpected circulatory arrest, occurring within an hour of symptom onset, or an unwitnessed, unexpected death without obvious noncardiac cause in patients known to have been well within the previous 24 hours. The mechanism is thought to be arrhythmic in most cases. SCD accounts for

TABLE 45.2 Strategies for Managing Sudden Cardiac Death Risk in Kidney Failure Patients

Strategy	Possible Intervention
Manage Underlying Cardiomyopathy	
Systolic heart dysfunction	Assess left ventricular systolic and diastolic function within 3 months of dialysis initiation and every 3 years thereafter.
	Use carvedilol in patients with dilated cardiomyopathy.
Diastolic heart dysfunction (left ventricular hypertrophy)	Consider frequent hemodialysis to reduce left ventricular mass; consider the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.
Minimize Arrhythmic Triggers	
Potassium shifts	Monitor potassium more frequently especially after hospitalization and change dialysis prescription accordingly.
	Avoid low (<2 mEq/L) potassium baths.
Calcium shifts	Avoid low calcium baths, especially in the context of concurrent use of QT-prolonging medications.
Metabolic alkalosis	Account for acetate in dialysis acid concentrate to determine total buffer; avoid high dialysate bicarbonate concentrations in patients who are alkalotic.
Rapid ultrafiltration	Encourage patient compliance with fluid restriction between treatments.
	Avoid sodium ramping and large dialysate/serum sodium gradients.
	Extend dialysis time to reduce ultrafiltration rate.
Dialysis-induced myocardial ischemia	Cool dialysate temperature
Weigh Benefits and Risks of ICDs	
	Consider secondary prevention ICDs after cardiac arrest.

ICD, Implantable cardioverter defibrillator.
Adapted with permission from Pun PH. The interplay between CKD, sudden cardiac death, and ventricular arrhythmias. *Adv Chronic Kidney Dis*. 2014;21(6):480–488.

about 25% of deaths among patients with kidney failure. As described earlier, very few of these events occur during dialysis, the majority occurring at home.

The optimal strategies to prevent SCD are not yet known (reviewed in Pun (2014)). Because SCD is thought to result from arrhythmogenic triggers (e.g., ECF changes, hypokalemia) acting on an arrhythmogenic substrate (underlying uremic and coronary heart disease), a sensible approach emphasizes optimizing treatment of underlying cardiac disease and minimizing dialysis-related arrhythmia triggers (Table 45.2). The role of ICDs in the prevention of SCD in kidney failure patients is at present unclear. It would seem reasonable to consider an ICD in dialysis patients who otherwise meet ICD criteria.

Digoxin Toxicity

Digoxin toxicity may manifest as atrial or ventricular ectopy, atrial fibrillation or atrial flutter, high-grade AV block, ventricular tachycardia, or ventricular fibrillation. Atrial flutter with 4:1 AV block is a classic presentation. Toxicity may result from an inappropriate dosage schedule in light of severely impaired excretion or concomitant use of drugs that increase digoxin levels (e.g., erythromycin, quinidine, verapamil, amiodarone). Acute lowering of serum potassium concentration during dialysis may further exacerbate toxicity. If suspected, digoxin should be stopped. Unstable rhythms need to be electrically cardioverted (ventricular tachycardia) or defibrillated (ventricular fibrillation). Stable ventricular arrhythmias can be treated with lidocaine or procainamide. Cardioversion should be avoided because of the risk of precipitating ventricular fibrillation in this setting. In severe cases, consideration should be given to antidigoxin Fab therapy. Often, superior alternatives to digoxin exist for chronic therapy of heart failure or arrhythmias (e.g., ACE inhibitors for congestive heart failure), and consideration should be given to switching to these alternative drugs.

Summary

Arrhythmias are frequent in dialysis patients. They are usually a reflection of underlying structural heart disease, which should be aggressively sought and treated. Mitigation of large or rapid swings in ECF volume and electrolyte composition

may minimize triggering of arrhythmias during dialysis, and the dialysis prescription should be modified accordingly in patients with dialysis-triggered arrhythmia or ectopy. Atrial fibrillation is the most prevalent arrhythmia in dialysis patients; however, the risk-to-benefit ratio of anticoagulation in nonvalvular AF is uncertain, and the decision to anticoagulate must be individualized and incorporate patient preferences. The role of ICDs in the prevention of fatal ventricular arrhythmias/SCD is not yet clear.

Recommended Reading

ACLS guidelines; 2015. https://www.acls.net/aclsalg.htm.

This website gives access to the latest algorithms for advanced cardiac life support.

Clase CM, Holden RM, Sood MM, et al. Should patients with advanced chronic kidney disease and atrial fibrillation receive chronic anticoagulation? *Nephrol Dial Transplant.* 2012;27(10):3719–3724.

A balanced analysis of the benefits, harms, and treatment uncertainties surrounding the question of anticoagulation for stroke prevention in dialysis patients with AF.

Zimmerman D, Sood MM, Rigatto C, Holden RM, Hiremath S, Clase CM. Systematic review and meta-analysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis. *Nephrol Dial Transplant.* 2012;27(10):3816–3822.

A comprehensive review of the epidemiology of this common rhythm in dialysis patients.

Al-Khatib SM, Allen LaPointe NM, et al. Rate- and rhythm-control therapies in patients with atrial fibrillation: a systematic review. *Ann Intern Med.* 2014;160(11):760–773.

An excellent synthesis of the evidence comparing these two strategies for management of AF.

Lehrich RW, Pun PH, Tanenbaum ND, Smith SR, Middleton JP. Automated external defibrillators and survival from cardiac arrest in the outpatient hemodialysis clinic. *J Am Soc Nephrol.* 2007;18(1):312–320.

A seminal study describing the incidence and risk factors for cardiac arrest in the dialysis unit.

Pun PH. The interplay between CKD, sudden cardiac death, and ventricular arrhythmias. *Adv Chronic Kidney Dis.* 2014;21(6):480–488.

A balanced overview of sudden cardiac death in CKD patients, including suggested preventive measures.

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Management of Ischemic Heart Disease, Heart Failure, and Pericarditis in Patients Undergoing Long-Term Dialysis

IAN E. McCOY, MD, MS

Introduction

Cardiovascular disease is exceedingly common in patients with kidney failure on maintenance dialysis and is the leading cause of death in this patient population. The rate of cardiovascular death in patients with kidney failure is substantially higher than that of the general population at all ages, but the disparity is particularly prominent within younger age groups. Cardiovascular disease is also a major contributor to the total morbidity of patients undergoing dialysis.

This chapter discusses the diagnosis and management of ischemic heart disease, heart failure, and pericarditis in patients with kidney failure undergoing dialysis. Recommendations based on evidence taken directly from the kidney failure population are discussed where possible. However, because the management of cardiovascular disease in patients with kidney failure has been relatively understudied and evidence from randomized clinical trials is limited, data from observational studies are included where necessary.

Ischemic Heart Disease

The prevalence of ischemic heart disease in patients on dialysis is estimated at 40%–50%. Also known as coronary artery disease, ischemic heart disease in patients on dialysis tends to be diffuse and multivessel and to have a high degree of calcification. The rate of acute myocardial infarction in patients on dialysis far exceeds the rate in the general population. The rate of acute myocardial infection in patients on dialysis was 73.1 per 1000 patient-years in 2011, compared to the rate in the general population of approximately 2 per 1000 patient-years. The high rates of ischemic heart disease in patients with kidney failure stem from the high prevalence of traditional and nontraditional risk factors (Table 46.1).

Clinical Presentation

Patients with kidney failure can have typical presentations of stable ischemic heart disease (e.g., dyspnea or chest pain with exertion) or acute myocardial infarction (e.g., substernal chest pain and diaphoresis). However, they often present atypically with symptoms, such as epigastric pain, fatigue, or nausea, perhaps due in part to the high prevalence of concomitant diabetes mellitus or uremia-related neuropathies. Only 44% of dialysis patients complain of chest pain during acute myocardial infarction (compared with 68% of non-dialysis patients). Moreover, symptoms and signs of acute coronary syndrome can be mistakenly attributed to complications of dialysis or kidney failure, leading to its underrecognition. Therefore, a high index of suspicion is needed for an accurate diagnosis of ischemic heart disease and acute coronary syndromes.

Diagnosis

The hemodialysis procedure is a kind of "stress test" that can precipitate symptoms of ischemic heart disease. A variety of factors contribute to this phenomenon, including tachycardia, dialysis-related hypoxemia, and intradialytic hypotension. The emergence of symptoms of ischemic heart disease on dialysis is an indication for further evaluation.

One-third to over one-half of patients with kidney failure have significant ischemic heart disease (>50% stenosis) by coronary angiography, despite having no symptoms.

TABLE 46.1 Risk Factors for Cardiac Disease in Dialysis Patients

Traditional	Nontraditional
Hypertension	Anemia
Dyslipidemia	Chronic inflammation
Diabetes	Oxidative stress
Smoking	Disordered bone and mineral metabolism
Sedentary lifestyle	Accelerated vascular calcification
Advanced age	Fluid overload
Left ventricular hypertrophy	Arteriovenous fistulae

However, routine screening for ischemic heart disease in asymptomatic patients with kidney failure is generally not indicated because randomized trials (albeit in populations without kidney failure) have shown that coronary revascularization in asymptomatic patients does not reduce cardiovascular morbidity or mortality, except possibly in patients with unprotected left main disease. Moreover, kidney failure is considered an ischemic heart disease risk equivalent with indications for maximal medical management and, therefore, not reliant on the results of screening tests.

One notable exception is potential kidney transplant recipients, who often undergo noninvasive stress testing and subsequent revascularization. To date, there has been only one randomized trial of coronary revascularization in asymptomatic patients with kidney failure awaiting kidney transplantation, all of whom also had diabetes mellitus. Manske et al. randomized 26 patients with documented significant coronary lesions by angiography to medical management or revascularization; 10 of 13 patients in the medically treated group and 2 of 13 patients in the revascularization group experienced the composite cardiac endpoint of unstable angina, acute myocardial infarction, or cardiac death during a median of 8 months of follow-up ($P = 0.002$). However, this study was conducted more than 25 years ago, and the medical management group received only aspirin and calcium channel blockers, making it difficult to apply these results to contemporary clinical practice. Despite the weakness of the available evidence, most clinical practice guidelines support screening asymptomatic patients awaiting kidney transplant who have additional risk factors, such as diabetes mellitus, known history of ischemic heart disease, older age, or longer dialysis vintage for ischemic heart disease with noninvasive testing followed by revascularization, if warranted. However, there is little consensus on the optimal timing for repeated screening tests, with some guidelines favoring annual testing, some recommending testing every 24 months, and others giving no specific interval for repeated testing. Some answers may be provided by the ongoing CARSK (Canadian Australasian Randomized Trial of Screening Kidney Transplant Candidates for Coronary Artery Disease) trial. After the CADScreening pilot trial demonstrated feasibility in 144 patients, the CARSK trial will randomize 3306 asymptomatic patients awaiting kidney transplant to noninvasive stress testing every 1–2 years or not (NCT03674307). Trial completion is projected for 2023.

Cardiac Troponins

Up to 70% of asymptomatic patients with kidney failure have chronic elevations of cardiac troponins (troponin T and troponin I). These chronic elevations do not seem to be due solely to decreased kidney clearance, as troponins are large molecules that would not be filtered intact by the kidney. Moreover, the elimination of troponins after an acute myocardial infarction is similar in patients with and without kidney failure. Instead, the troponin elevations seen in asymptomatic patients with kidney failure may reflect subacute ischemia, underlying cardiac structural disease, or recurrent myocardial stunning. Troponin elevations in patients on dialysis are associated with a two to fourfold higher risk of all-cause mortality, cardiovascular mortality, and major adverse cardiovascular events, and the U.S. Food and Drug Administration approved troponin T testing in patients with kidney failure for purposes of cardiac risk stratification over a decade ago. However, how best to use troponin values for clinical risk stratification and prognostication in stable patients with kidney failure remains unclear.

For diagnosis of acute myocardial infarction, cardiac troponins are the standard biomarkers, but their interpretation in patients with kidney failure is complicated by the high prevalence of chronically elevated values. A majority of patients with kidney failure have high-sensitivity troponin values greater than the 99th percentile of a normal reference population at baseline. The National Academy of Clinical Biochemistry recommends using a change of $\geq 20\%$ in troponin values 6–9 hours after presentation with ≥ 1 value exceeding the 99th percentile to define acute myocardial infarction in patients with kidney failure. However, a systematic review found little evidence to support this recommendation and could not identify clear cut-points that would maximize sensitivity and specificity and thus the positive and negative predictive values for cardiac troponins to diagnose acute myocardial infarction in kidney failure. Thus, troponins alone cannot be used to diagnose an acute myocardial infarction but rather should be placed in the broader context of presenting symptoms, electrocardiographic (ECG) findings, and other clinical factors.

Noninvasive Stress Testing

Exercise ECG has been the traditional method of noninvasive diagnosis of ischemic heart disease. The sensitivity of this test is only 50%–60% for single-vessel disease but is greater than 85% for triple-vessel disease in the general population. These figures are based on the assumption that the patient reaches an adequate exercise level (i.e., 85% of the age-adjusted predicted maximal heart rate). A large proportion of patients

with kidney failure are unable to achieve this target because of poor exercise tolerance or the use of beta-blockers, and many have abnormal baseline ECGs. Therefore, pharmacologic agents with imaging are often used for noninvasive testing in these patients.

The sensitivity of radionuclide testing in kidney failure patients ranges from 29% to 92%, with a specificity of 68%–88%. Dobutamine stress echocardiography may be the method of choice, as it avoids radiation exposure, has comparable sensitivity, and specificity in patients with kidney failure (35%–89% and 71%–94%, respectively). Patients with kidney failure have a much higher prevalence of coronary artery calcification compared to age-matched controls, which can be measured using electron beam computed tomography (EBCT). Studies of EBCT in patients with kidney failure have shown that higher coronary artery calcification scores are associated with higher risks of death and cardiovascular events. However, patients with kidney failure often have medial, rather than intimal, calcification, which may not have a causative role in ischemic heart disease. EBCT and other tests such as coronary CT angiography, coronary flow reserve assessment using positron emission tomography, and hybrid imaging approaches require further study in patients with kidney failure before they can be routinely used to screen for ischemic heart disease.

Coronary Angiography

Coronary angiography remains the gold standard for the diagnosis of ischemic heart disease. The major side effects associated with this procedure in dialysis patients are the potential precipitation of pulmonary edema due to volume overload and possible nephrotoxicity in patients with residual kidney function. The risk of both of these complications is minimized with the use of smaller volumes of contrast. In general, however, coronary angiography should be limited to those patients who have persistent symptoms of myocardial ischemia despite maximal medical therapy and in whom revascularization would be considered reasonable.

Medical Management

The treatment for acute coronary syndrome in patients with kidney failure is similar to that of the general population and includes timely administration of aspirin, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers (ARBs), and nitroglycerin, provided that there are no contraindications. Antithrombotic agents are often administered, particularly prior to percutaneous coronary interventions (PCIs), but special care to avoid renally cleared agents is required to reduce bleeding risks. A 2009 study showed that 22% of patients on dialysis undergoing PCI received a contraindicated antithrombotic agent (e.g., enoxaparin or eptifibatide), which was associated with a significantly higher risk of major in-hospital bleeding. Alternative antithrombotic agents are unfractionated heparin, abciximab, or bivalirudin.

For stable ischemic heart disease, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines, published in 2005, recommend treating patients on dialysis in the same way as for the general population: aspirin, beta-blockers, ACE inhibitors or ARBs, and statins. However, the evidence on which these guidelines are based is weak (level C), as many studies are observational rather than randomized trials, and not all studies focused exclusively on secondary prevention. Consequently, whether to use these agents in patients with established stable ischemic heart disease requires individual risk-benefit assessments by the physician and the patient.

Aspirin

Patients with kidney failure have a higher risk of bleeding complications due to uremic platelets, chronic inflammation, or repeated exposure to anticoagulation. In fact, two large observational studies, one using data from 41,425 patients in a large dialysis organization and the other a study of 28,320 patients from the DOPPS (Dialysis Outcomes and Practice Patters Study), showed higher risks of death and cardiac events in patients taking aspirin compared with patients not taking aspirin. However, given the nonrandomized nature of these studies, confounding by indication remains a concern.

Antihypertensive Medications

Optimal blood pressure targets have yet to be defined in hemodialysis. In contrast to the general population, where there is a linear relationship between systolic blood pressure and mortality in the dialysis population, a U-shaped curve is seen with a predialysis systolic blood pressure of 165 mm Hg associated with the lowest mortality risk. However, the potential for confounding from other factors such as heart failure is high in this observational data. The only randomized trial of blood pressure targets in kidney failure to date, the BID (Blood Pressure In Dialysis) pilot study, which randomized 126 patients on hemodialysis to predialysis systolic blood pressure targets of 110–140 mm Hg versus 155–165 mm Hg, was not powered for outcomes. Latest clinical guidelines recognize this lack of evidence and do not define a blood pressure target. Despite the lack of evidence on blood pressure targets, several randomized trials and two meta-analyses have shown that treatment with medications that lower blood pressure is beneficial to patients on dialysis.

Treatment with beta-blockers in patients on dialysis with stable ischemic heart disease to reduce cardiovascular morbidity and mortality remains uncertain. Results from observational studies have been mixed. One of the largest studies used data from 11,142 patients from the DMMS (Dialysis Morbidity and Mortality Studies) waves 3 and 4 and showed that beta-blocker use was associated with a 16% (confidence interval [CI], 7%–25%) lower risk of all-cause mortality. In contrast, several other observational studies showed no benefit associated with beta-blocker use in patients on hemodialysis. In the HDPAL (Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril)

study, patients on hemodialysis with left ventricular hypertrophy and hypertension randomized to an atenolol-based regimen had lower rates of heart failure and other cardiovascular events compared with patients receiving a lisinopril-based regimen. However, this was a relatively small study (200 patients) with predominately African American patients (86%), necessitating replication in larger, more diverse dialysis populations.

There have been several randomized clinical trials of ACE inhibitors or ARBs in patients on hemodialysis. A recent meta-analysis of these trials showed a definite benefit in terms of reduction in left ventricular mass ($p < 0.001$), but the association with reduction of cardiovascular events was not statistically significant (pooled rate ratio [RR], 0.66; CI, 0.35–1.25). Given these data, along with the reported benefit of ACE inhibitors or ARBs on the preservation of residual kidney function, ACE inhibitors and ARBs are recommended for patients with kidney failure.

Use of aldosterone-receptor blockers has also been examined in kidney failure. DOHAS (Dialysis Outcomes Heart Failure Aldactone Study) randomized 300 oligoanuric patients on hemodialysis to receive 25 mg/day of spironolactone or control. After 3 years of follow-up, the spironolactone group had a significantly lower risk of death and cardiovascular and cerebrovascular events (hazard ratio [HR], 0.4; CI, 0.2–0.7) compared with the controls. Serious hyperkalemia leading to discontinuation occurred in three patients (1.9%), all in the spironolactone group. However, the study was underpowered, open label, and had no placebo control. More recently, two small placebo-controlled studies, SPIN-D (Spironolactone in Dialysis) and MIRENDA (Mineralocorticoid Receptor Antagonists in End-Stage Renal Disease) have provided reassuring evidence on the safety of this intervention. Two large-scale efficacy trials are ongoing: ALCHEMIST (ALdosterone antagonist Chronic HEModialysis Interventional Survival Trial, NCT01848639) randomizing 825 patients on hemodialysis, and ACHIEVE (Aldosterone bloCkade for Health Improvement EValuation in End-stage Renal Disease, NCT03020303) randomizing 2750 patients on hemodialysis or peritoneal dialysis are both planned for completion in 2023–24.

Lipid-Lowering Medications

The 2013 Kidney Disease: Improving Global Outcomes (KDIGO) lipid management guidelines recommended that adults with kidney failure not initiate treatment with statins or statin/ezetimibe combination, given the results of three large-scale randomized clinical trials that failed to show a benefit in this population. The 4D Study (Die Deutsche Diabetes Dialyse Studie) randomized 1255 patients on hemodialysis with diabetes mellitus to receive atorvastatin 20 mg or placebo. Even though the impact on cholesterol reduction was similar to that observed in the general population, atorvastatin had no statistically significant effect on the primary composite endpoint of death from cardiac causes, fatal stroke, nonfatal myocardial infarction, or nonfatal stroke (RR, 0.92; CI, 0.77–1.10). AURORA (A study to evaluate the Use of Rosuvastatin in Subjects On Regular dialysis: An assessment of survival and cardiovascular events) randomized 2776 patients on hemodialysis to rosuvastatin 10 mg or placebo. Again, despite a reduction of 43% in low-density lipoprotein in the intervention group, no benefit was seen in the primary combined endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (HR, 0.96; CI, 0.84–1.11). Finally, the SHARP (Study of Heart and Renal Protection) randomized 9270 patients with advanced CKD (3023 of whom were on dialysis) to receive simvastatin 20 mg + ezetimibe 10 mg or placebo. Although a significant reduction in the rate of the primary outcome of major atherosclerotic events was seen in the intervention group overall, no benefit of active treatment was seen for the subgroup of patients on dialysis.

In patients who are already using statins prior to initiation of dialysis, the 2013 KDIGO guidelines suggest that these medications can be continued, although the evidence on which these suggestions are based is graded as low quality. In a departure from previous guidelines, after an initial lipid panel measurement, repeated follow-up lipid measurements are not recommended for most patients.

Bone and Mineral Metabolism

There is considerable experimental and clinical evidence that the disordered calcium metabolism and hyperparathyroidism associated with uremia contribute to left ventricular dysfunction, atherosclerosis, myocardial ischemia, and vascular and cardiac calcification. Observational data indicate that hyperphosphatemia and raised calcium × phosphate products are independently associated with mortality, especially death from ischemic heart disease and sudden death. The appropriate use of vitamin D analogs and phosphate binders is recommended to achieve target levels for serum calcium and phosphate. Phosphate binders are generally divided into two categories: calcium based (e.g., calcium acetate, calcium carbonate) or non–calcium based (e.g., sevelamer, lanthanum, or iron based). Several meta-analyses comparing calcium-based versus non-calcium-based phosphate binders have shown significant reduction in all-cause mortality for patients on dialysis receiving non-calcium-based phosphate binders.

Calcimimetic agents like cinacalcet are quite effective in lowering serum parathyroid hormone levels in patients with secondary hyperparathyroidism, but until recently, their effects on cardiovascular outcomes had not been studied. In 2012, results of the EVOLVE (Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events) trial were published. In this multicenter, prospective study, 3883 patients with kidney failure on hemodialysis with moderate to severe secondary hyperparathyroidism were randomized to receive cinacalcet or placebo, along with conventional therapy with phosphate binders, vitamin D sterols, or both. In the intention-to-treat analysis, the cinacalcet group had a relative hazard for death or first nonfatal cardiovascular event (the primary composite endpoint)

of 0.92 (CI, 0.85–1.02). However, after accounting for the high rates of study-drug discontinuation in both arms with lag censoring at 6 months after discontinuation, cinacalcet use had a nominally significant effect on lowering the risk of the primary composite endpoint compared with placebo (HR, 0.85; CI, 0.76–0.95).

Anemia

Anemia has been associated with left ventricular hypertrophy, development of de novo cardiac failure, and death in patients on dialysis. Partial correction of severe anemia is associated with improvement in left ventricular hypertrophy and exercise-mediated cardiac ischemia. Complete normalization of hemoglobin is not recommended, based on several clinical trials in kidney failure and CKD cohorts demonstrating a lack of significant clinical benefit but increasing risk of adverse cardiovascular outcomes and death. In 2012, KDIGO recommended evaluating iron status and supplementing with iron prior to initiation of an erythropoiesis-stimulating agent (ESA), which can be done when the hemoglobin falls below 9.0 g/dL. Targeting hemoglobin levels of 10.0–11.5 g/dL is generally appropriate for most patients on hemodialysis.

Coronary Revascularization

The indications for coronary revascularization in patients on dialysis are generally the same as those in the population without kidney failure (i.e., failure of medical therapy to control symptoms, significant left main disease, or triple-vessel coronary disease, particularly in patients with reduced left ventricular ejection fraction). However, clinical trials of revascularization often exclude patients with CKD, who have higher rates of in-stent thrombosis, restenosis, and bleeding. The ISCHEMIA-CKD (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches–Chronic Kidney Disease) Trial, published in early 2020, randomized 777 patients with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (including 53% on dialysis) and moderate or severe ischemia on stress testing, all of whom received optimal medical therapy, to an invasive or conservative strategy group. All patients in the invasive strategy group underwent cardiac catheterization followed by revascularization, while patients in the conservative strategy group received cardiac catheterization only after failure of optimal medical therapy. After a median follow-up of 2.2 years, there was no difference in the primary composite endpoint of death or nonfatal MI (adjusted HR, 1.01; 95% CI, 0.79–1.29; $p = 0.95$), but rates of stroke (HR, 3.76; 95% CI, 1.52–9.32; $p = 0.004$) and a composite of death or dialysis initiation (HR, 1.48; 95% CI, 1.04–2.11; $p = 0.03$) were higher with the invasive strategy.

There have been no randomized trials comparing coronary artery bypass grafting (CABG) with PCI in patients on dialysis, but observational studies have suggested a benefit in terms of lower risks of death and death or repeat myocardial infarction in patients on hemodialysis undergoing multivessel coronary revascularization. However, the perioperative mortality of CABG in patients on dialysis is roughly three times the expected rate for patients without kidney failure, and overall survival following any kind of coronary revascularization is much lower than for the general population. For patients who opt for PCI, the type of stent (i.e., drug-eluting vs. bare-metal) has not been adequately studied in patients with kidney failure. Current guidelines recommend drug-eluting stents based on observational studies and lower rates of restenosis observed in the general population. However, as drug-eluting stents require longer duration of dual antiplatelet therapy than bare-metal stents do for patients at high risk of bleeding or patients with planned upcoming major surgery (e.g., kidney transplantation), bare-metal stents may be preferred. Therefore, patients should have careful counseling with a multidisciplinary team of nephrologists, cardiologists, and surgeons in order to make informed decisions about optimal methods of coronary revascularization.

Hemodialysis-Related Interventions

Whether more hemodialysis improves cardiovascular outcomes have been a topic of interest for several years, and there have been randomized clinical trials aimed at answering this question. One study was the landmark Hemodialysis (HEMO) Study. The HEMO study randomized 1846 patients on thrice-weekly hemodialysis to a standard dose (single-pool Kt/V urea = 1.3) or high dose (single-pool Kt/V urea = 1.67) of dialysis. There were no differences in the primary outcome of all-cause mortality or any of the prespecified secondary outcomes, including cardiac hospitalization or cardiac death. The dialysis sessions in the high-dose group were approximately 30 minutes longer on average than in the standard dose group (219 minutes vs. 190 minutes).

More recently, the FHN (Frequent Hemodialysis Network) Trial randomized 245 patients with kidney failure to receive conventional, thrice-weekly hemodialysis or frequent in-center hemodialysis (6 times/week) for 12 months. Patients in the conventional hemodialysis arm had an average session length of 213 minutes (10.4 hours/week), whereas patients in the frequent hemodialysis arm had an average session length of 154 minutes (12.7 hours/week). Results showed that patients in the frequent-hemodialysis group had a lower risk of the primary composite outcome of death or increase in left ventricular mass (HR, 0.61; CI, 0.46–0.82), as well as improved hypertension control (a prespecified secondary outcome).

The FHN Nocturnal Trial randomized 87 patients to conventional thrice-weekly hemodialysis or frequent nocturnal home hemodialysis (six times per week). Patients in the conventional hemodialysis arm had an average session length of 256 minutes (12.6 hours/week), whereas patients in the frequent nocturnal hemodialysis arm had an average session length of 379 minutes (30.8 hours/week). No significant difference in death or left ventricular mass was

seen between the two groups, but patients in the frequent nocturnal hemodialysis arm had improved hypertension control (a prespecified secondary outcome). However, the study had difficulties with recruitment, resulting in a relatively small sample size and reduced power.

Lifestyle Modification

As with the general population, lifestyle modification for patients with kidney failure also has a role in ischemic heart disease management. Any patients with kidney failure who smoke should be encouraged to quit. Although some data suggest that increased muscle mass confers a survival advantage over fat, weight loss in patients with kidney failure is controversial, given the paradoxically lower risk for death for heavier patients. Therefore, a gradual exercise program with the goal of increasing muscle mass and cardiovascular health can be encouraged in patients with kidney failure on dialysis. Obese patients who are planning to undergo kidney transplants should be encouraged to lose weight.

Heart Failure

Heart failure is the most common cardiovascular diagnosis in patients with kidney failure. It is estimated that approximately 44% of patients on hemodialysis have heart failure. The associated risk for death is high, with 2-year mortality rates estimated at 49% for patients on hemodialysis in 2013. Disorders of left ventricular structure and function are highly prevalent in the dialysis population and begin long before dialysis therapy initiation. As with ischemic heart disease, the etiology of cardiac dysfunction leading to heart failure in kidney failure is partly attributable to the high prevalence of traditional cardiac risk factors but also to the metabolic and hemodynamic changes associated with kidney failure (Table 46.1).

Approximately 80% of patients starting maintenance dialysis have left ventricular hypertrophy or systolic dysfunction. In patients with diastolic dysfunction, heart failure results from impaired ventricular relaxation because of concentric or eccentric left ventricular hypertrophy. This leads to an exaggerated increase in left ventricular end-diastolic pressure for a given increase in end-diastolic volume. As a result, a small excess of salt and water can rapidly lead to a large increase in left ventricular end-diastolic pressure—culminating in pulmonary edema and symptomatic heart failure. In dilated cardiomyopathy, cardiac output is maintained at the expense of an increase in both end-diastolic fiber length and end-diastolic volume. As ventricular volume increases, inadequate hypertrophy leads to an increase in wall stress and an increase in end-diastolic pressure, also leading ultimately to pulmonary edema.

Diagnosis

The clinical signs of heart failure are the same for patients on dialysis as for the general population: dyspnea, jugular venous distention, bilateral lung crackles, and a characteristic chest radiograph appearance. Although heart failure is often attributed to "volume overload" in the dialysis patient, the appearance of such symptoms suggests an underlying cardiac abnormality. Echocardiography remains the method of choice for assessment of left ventricular geometry and function. In addition, echocardiography can diagnose valvular lesions that can contribute to cardiac dysfunction. NKF KDOQI guidelines recommend that all patients get an echocardiogram at initiation of dialysis after achieving their dry weight (because calculation of left ventricular mass and volume are affected by volume status), preferably on a nondialysis day, and then routinely every 3 years or when there is a change in clinical status.

As with cardiac troponins, B-type natriuretic peptide (BNP) is often chronically elevated in patients with kidney failure. In fact, some studies have shown that NT-proBNP (an inactive fragment of BNP) can be elevated in up to 99% of patients on hemodialysis and is therefore of limited diagnostic usefulness in this population. Elevated NT-proBNP levels are associated with the presence of left ventricular hypertrophy, reduced left ventricular function, and higher risks of death and cardiovascular events. However, because the levels of NT-proBNP can vary within and between individuals, its precise role in providing additional prognostic information remains to be defined in future studies before its routine measurement can be recommended.

Management

For all patients with symptoms of heart failure, potentially reversible precipitating and aggravating factors (i.e., ischemia, tachycardia, arrhythmias, or hypertension) should be sought and managed appropriately.

Volume Control

Diuretics are an essential component of the symptomatic treatment of heart failure in populations without kidney failure but are of more limited value for patients on maintenance dialysis. Loop diuretics should be continued as long as the patient continues to have residual kidney function. For all patients on dialysis, but particularly those patients with established heart failure, maintenance of an accurate dry weight is essential. Some patients may require more frequent or prolonged hemodialysis sessions to achieve adequate volume removal. Heart failure may be exacerbated by a high-flow arteriovenous fistula, and banding or revision of the fistula may improve symptoms.

Sodium intake should also be monitored in order to reduce interdialytic weight gain, and patients should be counseled to consume no more than 2–3 g of sodium per day. Some guidelines suggest even lower daily sodium intake (< 1500 mg/day), but this recommendation remains somewhat controversial. The use of lower dialysate sodium baths and discontinuation of sodium modeling have been advocated as ways to reduce the total sodium load experienced by patients after a hemodialysis session. However, optimizing

sodium dialysate prescriptions to minimize sodium exposure without precipitating intradialytic hypotension remain an area of active investigation.

Antihypertensive Medications

Beta-blockers are widely used in the management of heart failure with left ventricular systolic dysfunction in the general population as a result of studies showing improvement in mortality and morbidity. Current guidelines for the general population suggest the routine use of beta-blockers in clinically stable patients with a left ventricular ejection fraction ≤40% and mild to moderate heart failure symptoms who are on standard therapy (i.e., diuretics, an ACE inhibitor, and digoxin). Such therapy should also be considered for asymptomatic patients with a left ventricular ejection fraction >40%, but the evidence supporting its use in this setting is not as strong.

To date, there has only been one randomized clinical trial of beta-blockers in patients on hemodialysis with heart failure. That study randomized 114 patients on hemodialysis with dilated cardiomyopathy to receive carvedilol or placebo in addition to standard therapy. After 2 years, treatment with carvedilol reduced the risk of death from any cause (52% vs. 73%, $p < 0.01$) and cardiovascular death in particular (29% vs. 68%, $p < 0.00001$).

This, along with numerous observational data, supports the notion that beta-blockers may be safely used in the dialysis population in the same manner recommended for the general population. As in the nondialysis population, these agents should be started in low doses with careful clinical reevaluation during the titration phase. Beta-blockers with low dialytic clearance (such as carvedilol—negligible dialytic clearance) may be preferred. An observational analysis found that beta-blockers with high dialyzability (e.g., atenolol, metoprolol) were associated with a 1.4-fold higher mortality risk compared with poorly dialyzable beta-blockers (e.g., bisoprolol, propranolol). If highly dialyzed beta-blockers are used, they can be dosed three times a week after dialysis, as was shown to be effective for atenolol in the HDPAL trial.

In patients without kidney failure, several studies have confirmed the utility of ACE inhibitors and ARBs to improve symptoms, reduce morbidity, and improve survival. The NKF KDOQI guidelines, therefore, recommend ACE inhibitors or ARBs for treatment in patients with kidney failure, despite the fact that there are no trials in patients with established heart failure on dialysis. ARBs are not dialyzable and may be preferred over ACE inhibitors, which are removed with dialysis (with the exception of fosinopril).

In 2010, Cice et al. published the results of a 3-year trial that randomized 351 patients on hemodialysis with left ventricular ejection fraction ≤40% and heart failure (New York Heart Association functional class II to III) to receive telmisartan or placebo in addition to ACE inhibitor therapy. Results were impressive; the addition of telmisartan to standard therapy reduced death by 49% (CI, 18%–68%), cardiovascular death by 59% (CI, 49%–62%), and heart failure hospitalization by 62% (CI, 49%–81%). However, there was a higher frequency of adverse events in the telmisartan group, which was predominantly hypotension. It is also unclear how generalizable these results are to the entire dialysis population since these heart failure patients were all on four times a week hemodialysis. In contrast, a large observational study showed a significantly higher risk of cardiovascular mortality risk in patients on hemodialysis initiated on an ARB + ACE inhibitor, compared with patients initiated on an ARB + non-ACE inhibitor antihypertensive agent. These data suggest that combined ACE inhibitor and ARB therapy, taken together, can be considered in patients on hemodialysis with heart failure and systolic dysfunction, but with careful monitoring for possible adverse effects, including hypotension and hyperkalemia.

As noted earlier, the DOHAS trial showed a benefit of spironolactone compared to standard therapy on lower risks of death and cardiovascular and cerebrovascular events in patients on hemodialysis. However, despite the words "heart failure" in the trial name, DOHAS did not focus on recruitment of patients with kidney failure with established heart failure. Therefore, the use of aldosterone receptor blockers in kidney failure is not currently recommended as part of standard heart failure treatment in these patients.

Digoxin

Digoxin has been used in patients with kidney failure primarily for ventricular rate control in patients with heart failure and atrial fibrillation. However, there are significant safety concerns given the narrow therapeutic window, long half-life, and fluctuations in serum potassium levels that occur with hemodialysis. To date, there have been no randomized trials of digoxin in the kidney failure population. An observational study of 120,864 incident patients on hemodialysis showed a 28% higher risk of death (CI, 25%–31%) associated with digoxin use versus nonuse. These results were consistent in sensitivity analyses that limited the cohort only to patients with indications for digoxin (e.g., atrial fibrillation and/or heart failure). The high mortality risk was highest among patients with the lowest predialysis serum potassium levels. If used at all, digoxin in patients on hemodialysis with heart failure must be carefully monitored with drug levels and avoidance of hypokalemia. Digoxin should not be given to patients with primarily diastolic dysfunction, as the increased contractility could worsen diastolic impairment.

Device Therapy

Implantable cardioverter defibrillators (ICDs) used for primary prevention of serious arrhythmias in patients with left ventricular ejection fraction <35% have not been well studied in kidney failure. Their use is controversial given the high risk of infection (two to five times higher than the general population), risk of central stenosis from transvenous leads, and limited life expectancy. Subcutaneous ICDs may be a reasonable alternative to transvenous ICDs in this population. Left ventricular assist devices (LVADs) have

shown extremely poor results when placed in patients with kidney failure (median survival, 16 days versus 2125 days in patients without kidney failure).

Uremic Pericarditis

Because of the earlier initiation of dialysis and higher delivered dialysis doses, clinically significant uremic pericarditis is now a relatively rare event. When it does occur, the symptoms may be sudden and have severe consequences if not recognized and treated promptly. A high index of suspicion is therefore required. Between 50% and 70% of patients with uremic pericarditis will respond to initiation or intensification of dialysis, suggesting uremia itself is responsible in some cases. Cases that do not improve with dialysis may be due to other etiologies, such as viral pericarditis.

Clinical Presentation and Diagnosis

The typical clinical presentation of pericarditis may include precordial pain, dyspnea, cough, or fever. The chest pain is not related to exertion, may be pleuritic in nature, and is often relieved by leaning forward. Most patients will have a pericardial friction rub. Those patients with a significant pericardial effusion may have jugular venous distention or a paradoxical pulse. Any of these symptoms in the presence of new-onset hypotension makes pericardial tamponade a likely diagnosis. Electrocardiograph findings (classically diffuse ST changes in nonuremic pericarditis) are not sensitive or specific in uremic pericarditis. Echocardiography should be performed in any patient suspected of having a pericardial effusion to estimate its size and guide further management.

Management

For patients who are hemodynamically stable and without impending tamponade, intensification of dialysis and analgesia is usually all that is required for management. Fluid removal with dialysis should be limited and cautious given preload dependence and the potential for hypotension and cardiogenic shock. Pericardiocentesis can be considered if not improving after 7–14 days. Nonsteroidal anti-inflammatory drugs, used cautiously, are useful for reducing pain but do not appear to hasten the resolution of pericarditis. Prednisone is not recommended and may actually increase morbidity. Heparin should be avoided during dialysis therapy if at all possible to prevent hemorrhagic complications. Patients should be carefully monitored for clinical evidence of tamponade until all symptoms have resolved.

Hemodynamically unstable patients who have tamponade require immediate pericardiocentesis. Blind pericardiocentesis is associated with considerable risks and is therefore indicated only in the most urgent cases. Patients with a large pericardial effusion or those with unstable hemodynamics and/or echocardiographic evidence of cardiac-chamber compromise (even with a moderate pericardial effusion) should be referred for pericardiostomy, pericardial window, or pericardiectomy. The selection of the surgical procedure should be based on clinical and hemodynamic status, comorbid conditions, and the experience of the physician. Pericardial window is often the procedure of choice.

Recommended Reading

Bhatti NK, Karimi Galougahi K, Paz Y, et al. Diagnosis and management of cardiovascular disease in advanced and end-stage renal disease. *JAMA.* 2016;5(8):1–14.

A review of coronary artery disease, congestive heart failure, valvular disease, and pulmonary hypertension in ESRD.

Cice G, Benedett AD, D'Isa S, et al. Effects of telmisartan added to angiotensin-converting enzyme inhibitors on mortality and morbidity in hemodialysis patients with chronic heart failure. *J Am Coll Cardiol.* 2010;56(21):1701–1708.

A randomized double-blind placebo-controlled trial in patients on hemodialysis with heart failure showing that the addition of the ARB to standard treatment including an ACE inhibitor dramatically reduced the risk of death, cardiovascular death, and heart failure hospitalization.

Heerspink HJL, Ninomiya T, Zoungas S, et al. Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomized controlled trials. *Lancet.* 2009;373:1009–1015.

Comprehensive review of eight randomized trials of 1679 patients on dialysis, showing that blood pressure–lowering treatment was associated with lower risks of cardiovascular events, all-cause mortality, and cardiovascular mortality.

House AA, Wanner C, Sarnak MJ, et al. Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int.* 2019 Jun;95(6):1304–1317.

Review of up-to-date diagnosis and management strategies for heart failure in CKD including ESRD.

Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO Clinical Practice Guideline for lipid management in chronic kidney disease. *Kidney Int.* 2013;3(suppl):259–305.

Excellent evidence reviews and practice guidelines for lipid management for patients across all stages of chronic kidney disease, including patients on hemodialysis.

Sarnak MJ, Amann K, Bangalore S, et al. Chronic kidney disease and coronary artery disease: JACC state-of-the-art review. *J Am Coll Cardiol.* 2019;74:1823–1838.

Summary of the Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference on CAD and CKD (including end-stage kidney disease and transplant recipients).

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Avoidance and Treatment of Cardiovascular Disease in Dialysis

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Introduction

The prevalence and severity of cardiovascular disease in the dialysis population are well appreciated and present one of the defining therapeutic challenges in nephrology. It is also one of the most difficult issues to approach—the unique pathophysiologic processes underpinning disease in the dialysis population require specialized care, aimed at optimizing dialysis therapy and preventing cardiovascular injury associated with dialysis, and also consider the unique response to conventional medications/therapeutic approaches in this specialized patient population. These challenges present multiple pitfalls in the treatment of these patients. What may be considered a standard treatment, recognized to be effective in the general population, could potentially not only be ineffective but actually cause unintended harm. Furthermore, other specialist services may not always be aware of the specific challenges that apply to dialysis patients, making consulting with other specialties a not altogether straightforward process. It is therefore vital that nephrologists are fully informed of the hazards that can ensue in treating cardiovascular disease in their patients according to diagnostic and therapeutic evidence extracted from the non–chronic kidney disease (non-CKD) population. In recent years, mounting evidence has been published on the importance of nontraditional cardiovascular risk factors and the inefficacy of treatments designed for the general, non-CKD population; this serves to highlight the many uncertainties faced by a physician caring for a dialysis patient. An evolved understanding of these uncertainties may help prevent patients from receiving inappropriate investigations and treatments. Early evidence also provides potential ways to improve patient well-being, quality of life, and mortality outcomes.

Management of Cardiovascular Disease

The diagnosis, prevention, and treatment of cardiovascular disease in dialysis patients present several challenges. This is even more unfortunate given the high prevalence of cardiovascular disease and results from the unique combination of susceptibility and stressing factors experienced by dialysis patients.

Presentation and Diagnosis of Cardiovascular Disease

The presentation of acute coronary syndrome in dialysis patients is often atypical and may consist of shortness of breath, fatigue, or palpitations rather than classical central chest pain. A high index of suspicion is warranted in all dialysis patients presenting with otherwise unexplained symptoms; hospital admission should be considered at a low threshold to allow for the necessary investigations. However, nephrologists must always be aware that there are considerable challenges involved in applying and interpreting standard diagnostic tests.

Cardiac Enzymes

There are well-evidenced cutoffs for values of cardiac enzymes that, combined with increased assay sensitivity, are the bedrock of diagnosis for acute coronary syndromes in the general population. Increased values in high-sensitivity troponin assays are burdened by reduced specificity; the differential diagnosis of acute coronary syndrome includes heart failure, atrial fibrillation, aortic dissection, pulmonary embolism, myocarditis, cardiomyopathies, sepsis, and others. Acute kidney injury and CKD are also associated with increased troponin levels, with their levels being correlated with the degree of kidney dysfunction. This makes the diagnosis of acute coronary syndrome complicated when based on absolute values. The physiological mechanisms responsible for the degradation of troponins are still unclear and involve tissue fragmentation by serine proteases and tubular secretion. Recent evidence suggests that elevated serum troponin levels are not just the result of reduced kidney clearance but rather may be due to

increased cardiac release and signal subclinical myocardial injury. Diastolic dysfunction, left ventricular hypertrophy, coronary microvascular disease, and myocardial fibrosis may underlie chronically elevated serum troponin levels—indicative of "ventricular distress." These findings may partially explain the negative prognostic value of troponin levels in dialysis patients. Determining a "baseline" troponin value may be helpful for prognostic stratification and future comparisons; monitoring the biomarkers' evolution over a period of hours may have some utility where the diagnosis of acute coronary syndrome is uncertain. However, clearer, evidence-based recommendations are needed.

Electrocardiography

Interpretation of electrocardiograms (ECG) in dialysis patients is not always straightforward. Studies have suggested that hemodialysis (HD) in particular induces repolarization abnormalities that may interfere with parameters, such as the calculation of the QT interval, and indeed, longstanding cardiac morphologic changes often leave highly abnormal patterns of repolarization that masquerade (especially handicapping automated ECG reporting software) as acute changes. Having a recent baseline ECG to refer to is crucial in accurate interpretation in the setting of suspected acute cardiac events.

Exercise Stress Testing

Although exercise stress remains an integral part of the workup of transplantation candidates, its utility in the dialysis population is not proven. In terms of overall risk stratification, many patients, even those under consideration for transplantation, will be unable to complete an exercise test to the required heart rate because of physical frailty, mobility limitations, autonomic neuropathy, or medication preventing them from the development of an appropriate stress response. Exercise stress testing is a poor predictor of posttransplant outcomes. Most physicians will accordingly proceed to alternative tests in order to assess the patient for reversible ischemia.

Isotope Stress Testing

In terms of risk stratification, in the general population, isotope stress testing (using pharmacological means) can be of use in patients unable to complete an exercise stress test to the required heart rate. However, there is evidence that in dialysis patients, the sensitivity of myocardial perfusion scans to detect coronary artery disease is significantly reduced. In patients who have had a negative isotope stress test and then progressed to transplantation, a negative stress test is a poor predictor of which patients have gone on to have cardiovascular events. Although isotope testing again remains a standard tool in the transplantation workup, this poor predictive value should be borne in mind when counseling a patient for transplantation, and the result of an isotope stress test should be interpreted in the context of the patient's other symptoms and overall health.

Coronary Angiography

This remains the gold-standard investigation in the general population, but one that again is more difficult to apply in the dialysis population. The decision to go ahead with diagnostic and therapeutic coronary angiography is not always clear-cut. Although percutaneous intervention remains the treatment of choice in dialysis patients with an ongoing acute coronary syndrome, such as ST-elevation myocardial infarction (MI), many patients have cardiac events in the absence of significant stenotic lesions. Outside of an acute event, a significant proportion of symptomatic and high-risk (or higher risk as all patients regardless of age have a significantly elevated cardiovascular risk) individuals will have no treatable lesion identified (approximately 50% according to case series). Atheromatous coronary arterial disease is extremely common in dialysis patients, but the functional significance of individual lesions is much more difficult to determine. To determine the potential clinical significance of a lesion, further testing, such as the determination of fractional flow reserve, may be needed, but as yet, there is no evidence that such a directed approach improves outcomes. Aside from the diagnostic accuracy of the test, the use of iodinated contrast and subsequent impact on residual kidney function must also be considered. The decision to refer a patient for angiography should bear these realities in mind, and the potential benefits of this invasive procedure must be considered to outweigh the risks.

Prevention and Treatment Strategies

The evidence supporting pharmacologic therapies is currently limited, as dialysis patients are usually excluded from most major randomized controlled trials. Most recommendations are based on small and underpowered studies or expert opinions. Therefore, most standard treatments used in the general population lack solid evidence for efficacy and may be ineffective or harmful due to the pharmacokinetic properties of the employed drugs.

Antiplatelet Therapy

The use of antiplatelet medications in cardiovascular disease must always be balanced against the higher risk of bleeding due to uremic platelet dysfunction. In CKD as a whole, evidence derived from meta-analyses suggests that antiplatelet treatment reduces the incidence of MI but has no effect on cardiovascular or all-cause mortality and increases the risk of hemorrhagic stroke. Combination therapy with dual antiplatelets is particularly associated with higher serious hemorrhagic risk in kidney failure. Therefore, dual antiplatelet therapy after coronary percutaneous revascularization is

generally advised for short periods and is not advised when concomitant oral anticoagulants are prescribed. Evidence is lacking on the newest P2Y12 inhibitors, e.g., prasugrel and ticagrelor, and therefore favors the use of clopidogrel as the principal agent. Given the higher risk of major bleeding, care must be taken in prescribing these drugs appropriately.

Revascularization Therapy

Regardless of the method of revascularization, periprocedural mortality is higher than in the general population, and long-term survival is lower. Coronary artery bypass grafting currently has the highest long-term survival of the revascularization therapies. However, it also carries the highest initial morbidity and mortality, much higher than in the general population. These risks do not appear to be significantly modified by the use of more modern approaches to avoid cardiopulmonary bypass. Percutaneous interventions are associated with a lower initial mortality but also a lower long-term survival—the benefit of coronary artery stenting is attenuated in dialysis patients. Overall, there is little difference between the two interventions. The more limited efficacy of percutaneous coronary intervention is at least partly due to the type of lesions encountered in dialysis patients, the frequency of encountering multifocal lesions, and the proximal locations of these lesions. It should be noted that the requirement for dual antiplatelet therapy also poses hazards in the form of a higher risk of major bleeding. Again, a careful calculation of the relative risks and benefits must be performed before undertaking revascularization therapy. Intractable chest angina, resistant to conservative medical therapy, remains the most consistent indication for percutaneous coronary intervention in this group.

Statins

Following the failure of a number of smaller trials to show any effect on mortality from statin use in the dialysis population, the SHARP study (Study of Heart and Renal Protection, the largest trial of its type) was conducted in patients with CKD. A total of 3023 of these patients were receiving dialysis, and although a reduced incidence of stroke and arterial revascularization procedures was observed, no clear mortality benefit was found. At the time of writing, there is no convincing evidence that statins are of any benefit to dialysis patients in terms of primary or secondary prevention of coronary artery disease and cardiovascular mortality.

Blood Pressure Control

As stated by the 2019 Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference on Blood Pressure and Volume Management in Dialysis, there is no accepted definition of hypertension for patients on long-term dialysis. Additionally, there is no consensus on how blood pressure (BP) should be measured; 44-hour interdialytic ambulatory BP monitoring has shown the best prediction for major outcomes, followed by home BP and office BP. Conversely, pre- and postdialysis BP measurements have a poor value in predicting clinical outcomes. In this population, the prevalence of hypertension is estimated to be up to 80% as a result of the combination of volume overload and vascular stiffness (causing increased peripheral resistance).

The treatment of hypertension should focus initially upon achieving adequate extracellular volume (water and sodium) management (the optimal level of hydration is also not clear at present, but discussion of that is beyond the scope of this chapter). The Dry-Weight Reduction in Hypertensive Hemodialysis Patients (DRIP) randomized controlled trial showed that additional volume removal by probing the dialysis dry weight reduced BP in hypertensive patients on HD. This evidence is further reinforced by single-center experiences in Tassin (France) and Turkey, where the combination of extended treatment times and salt restriction achieved improved BP control, without antihypertensive medications, in over 90% of patients and was associated with better long-term survival.

Antihypertensive medications are commonly prescribed as an extension of the current hypertension guidelines. However, there is no evidence of what class of antihypertensive medications should be used, nor an accepted BP target to achieve. Only one pilot randomized controlled trial (Blood pressure In Dialysis, BID) thus far has tested the feasibility of intensive BP treatment (target systolic BP 110–140 mm Hg predialysis, either by probing the dry weight or with antihypertensive medications) versus standard of care (target 155–165 mm Hg predialysis). The trial was underpowered to show any effects on clinical outcomes, although it showed a significantly higher incidence of hospitalization and vascular access thrombosis in the intensive BP treatment arm. Therefore, at present, there is no solid evidence base demonstrating a benefit of intensive BP control to prevent cardiovascular events, with relevant safety signals associated with it. Care should be taken in prescribing antihypertensive medications; timing of administration and dialyzability of specific molecules (especially for beta-blockers) may play a part in reducing the hemodynamic tolerability to ultrafiltration or increasing the arrhythmogenic risk associated with HD. Furthermore, beta-blockers may be harmful in patients prone to bradyarrhythmias and asystole: an increasingly appreciated (and potentially predominant) cause of sudden cardiac death in HD patients. Patients also commonly suffer from autonomic neuropathy with decreased baroreceptor sensitivity, and this further decreases the compensation mechanisms to tolerate ultrafiltration. The combination of autonomic neuropathy and aggressive BP control with antihypertensive medications leaves patients more vulnerable to episodes of intradialytic hypotension during HD by further impairing their vasoregulatory reserve.

Nonosmotic Tissue Sodium Deposition and Management

Recent studies have suggested that sodium is stored in a nonosmotic fashion (i.e., without commensurate water

retention) at the skin level and the endothelial surface layer (glycocalyx), bound to highly, negatively charged glycosaminoglycans. Although the magnitude of these deposits is unclear in humans, these anatomical structures are thought to buffer sudden increases in plasma osmolarity and volume-dependent hypertension in response to acute sodium loading. At the interstitial level, sodium deposition is regulated by resident macrophages that are able to sense and modulate local tonicity by controlling lymphatic capillary density and lymphatic drainage. Sodium deposition at the endothelial surface layer seems implicated in endothelial dysfunction, arterial stiffness, and increased BP through the downregulation of endothelial nitric oxide synthase. Noninvasive tissue sodium quantification is possible through a novel imaging technique, sodium-23 magnetic resonance imaging (MRI). This technique can be applied to soft tissues of peripheral limbs and other target organs, such as the heart, the kidneys, and the brain. Age has been recognized as one of the most important determinants of tissue sodium concentration due to the age-dependent decline in cellular mass in favor of extracellular volume expansion, and an increase in tissue sodium has also been observed in patients on dialysis. HD has been shown to remove tissue sodium through convective and diffusive sodium clearance. Convection alone is known to produce a hyponatric ultrafiltrate due to the Gibbs-Donnan effect, as plasma proteins prevent a small fraction of sodium from crossing the dialyzer membrane to maintain electroneutrality. This is especially relevant when coupled with conventional, high-dialysate sodium HD, often resulting in positive intradialytic net sodium balance and increased total body tonicity, stimulating interdialytic thirst and weight gain. Lowering the dialysate sodium has been associated with reduced skin sodium concentration—improving intradialytic diffusive sodium clearance is essential to maintain the sodium balance. However, this intervention is associated with acute falls in plasma tonicity, often resulting in intradialytic hemodynamic instability in standard HD practice; it is, therefore, necessary to identify patients who may benefit from this intervention to personalize this treatment.

Hybrid Therapy

Single-center experiences have been advocating for the combination of peritoneal dialysis and HD to exploit the benefits of both techniques. In particular, peritoneal dialysis allows for slower, gentler ultrafiltration, reducing interdialytic weight gain as HD maintains solute and volume balance. Shifting from peritoneal dialysis alone to hybrid therapy has been associated with lower systolic BP and left ventricular mass, improved left ventricular systolic function, and volume control by decreasing the incidence of acute cardiovascular events. Furthermore, increasing diffusive sodium removal by administering low-sodium peritoneal dialysis solutions has been shown to reduce BP, extracellular volume, and thirst while maintaining stable sodium serum levels. Although current reports did not show a significant increase in dialysis access complications, a reasonable concern of hybrid therapy remains facing potential complications typical of both techniques.

Optimization of Kidney Replacement Therapy

Dialysis patients have deficient compensation mechanisms that make them vulnerable to the hemodynamic challenge of intradialytic volume removal. Several studies have shown that a standard 4-hour HD session leads to a reduction in myocardial blood flow in a significant number of patients. Similar changes have been recently observed in the brain and the kidneys as well. In the heart, this repetitive injury leads to a combination of recurrent acute ischemic episodes and cardiac remodeling, with irreversible regional systolic dysfunction and myocardial fibrosis. These changes may explain the high incidence of cardiac failure and sudden cardiac death (approximately 26% of dialysis patients). These recurrent injuries begin early in a patient's time on HD and continue to occur throughout the treatment lifetime. Kidney transplantation has been shown to partially reverse this injury, although the time spent on dialysis also affects adversely overall prognosis.

Recent studies have focused on the prevention of HD-induced cardiovascular injury by optimizing the dialysis procedure. Medical imaging-based surrogate outcomes, such as intradialytic myocardial perfusion and ultrasound-based speckle tracking imaging to quantify left ventricular contractile dysfunction, were used to provide detailed information on end-organ pathophysiology during dialysis. Interventions that have shown promise in small-scale trials include: prolonged and/or more frequent HD schedules to reduce ultrafiltration rates and improve uremic toxin removal; dialysate cooling to restore baroreflex sensitivity and improve vasoreactivity to hemodynamic stress; remote ischemic preconditioning, a procedure that induces a temporary and reproducible ischemia-reperfusion stimulus on a peripheral limb to produce a subsequent systemic and long-lasting protective response to an expected ischemic injury (e.g., HD); and intradialytic exercise, improving hemodynamic stability and producing an ischemic preconditioning-like response. Many of these interventions are simple and inexpensive, although they require further validation in large randomized controlled trials. Simple alterations to the dialysis procedure and further elucidation of the optimal fluid status offer potential hope for attenuating the ischemic injury of HD in the short term. There may also be room for more novel therapies that add a cardioprotective element to these adjustments.

Peripheral Vascular Disease

Pathophysiology

The relatively unique properties of vascular disease in patients on dialysis are an important reason that an alternative

approach and treatment are often required. The main features of vascular disease associated with CKD are endothelial dysfunction, inflammation, oxidative stress, and vascular calcification. These factors make dialysis patients prone to the development of atherosclerosis, resulting in arteriosclerosis and arterial stiffness and ultimately contributing to a prothrombotic state, impaired vasoregulation, and vulnerability to demand ischemia in a variety of critical organ systems, such as the heart and brain.

Endothelial Dysfunction

Endothelial dysfunction is common in CKD and is recognized as an early marker of atherosclerosis. It is an independent predictor of MI, heart failure, and death. Experimental evidence shows impaired endothelium-dependent vasodilatation and nitric oxide production in CKD patients. In particular, the equilibrium between endothelial injury and repair capacity is disrupted, favoring the former. Several traditional and nontraditional factors have been found to be associated with endothelial dysfunction. Among the nontraditional factors, uremic toxins, and especially protein-bound compounds such as indoxyl sulfate, *p*-cresyl sulfate, and advanced glycation end-products (AGEs) act as pro-oxidants, proinflammatorys, proatherogenics, and prothrombotics, while also increasing vascular smooth cell muscle proliferation. Oxidative stress, as an imbalance between the generation of oxidative compounds and their antioxidant regulatory mechanisms, leads to reactive oxygen species (ROS) generation and endothelial damage. The common metabolic phenotype of patients with CKD—associated with older age, diabetes, and hypertension—predisposes them to increased oxidative stress. This is compounded by the HD procedure itself, where antioxidant vitamins are lost through the dialysis procedure, and ROS are generated on the dialysis membrane due to suboptimal biocompatibility. The elevated generation of ROS is a major cause of endothelial dysfunction and microcirculatory malfunction. Recent experimental evidence also suggests that sodium overload may cause the endothelial surface layer (or glycocalyx) to stiffen, reducing its sodium buffering capacity and nitric oxide synthesis.

Uremic Toxins

As mentioned earlier, uremic toxins play an essential role in determining endothelial dysfunction, systemic inflammation, and cardiovascular disease progression. The European Uremic Toxin Work Group has published a database containing 130 compounds associated with accumulation and toxicity in CKD. Three classes of uremic toxins have been postulated, based on molecular weight and interactions: small, water-soluble uremic toxins (e.g., urea, creatinine), protein-bound uremic toxins (e.g., indoxyl sulfate, p-cresyl sulfate), and middle molecules (e.g., beta2-microglobulin, parathyroid hormone [PTH], interleukin-6 [IL-6], immunoglobulin light chains). Other mediators of uremic toxicity not mentioned in this classification include lipopolysaccharides (or endotoxin) and AGEs. The clinical implications of uremic toxins are highly complex; the protean manifestations of uremic toxicity are likely the result of the interaction between the various toxins, serum level interindividual variability, and individual susceptibility. A systematic review is beyond the scope of this chapter. Experimental evidence relating to the uremic cardiovascular toxicity of these compounds has shown that vascular exposure to uremic plasma-induced endothelial dysfunction and increased vascular permeability. Furthermore, several studies have found an association between endotoxin and protein-bound uremic toxins with HD-induced hemodynamic stress, systemic inflammation, cardiovascular disease, and mortality.

Many of these mediators are synthetized by the gut microbiota; intestinal dysbiosis associated with CKD and HD-induced intestinal and hepatic ischemic injury alters the gut mucosal permeability and induces a transient hepatic metabolic dysfunction, increasing endotoxin and protein-bound toxin translocation into the systemic circulation. This process likely exacerbates uremic toxicity and is clinically translated into uremic symptoms and progressive cardiovascular disease.

Accumulation of AGE is also of interest in the CKD and dialysis populations. AGEs accumulate in the tissues by covalent, nonenzymatic reaction between reducing sugars and free amino groups of proteins, lipids, and nucleic acids. Although diabetes is traditionally recognized as the main determinant of AGE formation, CKD is also associated with AGE accumulation due to reduced kidney excretion, increased oxidative stress, and increased precursor compound levels. Dietary AGE intake and tobacco smoking also contribute to increased tissue AGE levels. AGE tissue levels, measured noninvasively by skin autofluorescence, were found to increase progressively as CKD stage worsened. Tissue AGE levels were associated with a higher risk of cardiovascular events and mortality in nondialysis CKD patients, providing yet another potential target for novel clinical interventions.

Vascular Calcification

Vascular calcification is highly prevalent in patients with CKD, and studies using computed tomography (CT) have suggested a prevalence of greater than 80% in kidney failure patients. The mechanisms are multifactorial and incompletely understood. Calcium can be deposited in the medial or intimal layers of the vessels, although the hallmark of vascular calcification in patients with CKD is diffuse medial calcification as a result of direct ossification of the vessel. The administration of calcium-based phosphate binders has been associated with higher risk of vascular calcification, therefore discouraging their use in favor of other calcium-free phosphate binders. Risk factors for vascular calcification include dialysis vintage, older age, hyperphosphatemia, high dialysate calcium, high calcium-phosphate product, diabetes, vitamin D therapy, and inhibitors of

vitamin K, such as warfarin. Detection and quantification of vascular calcification have not gained traction in routine care, largely because of a lack of specific therapy to reverse it.

Inflammation

Kidney failure patients exhibit persistent subclinical inflammation, enhanced by multiple factors such as reduced inflammatory mediator clearance, dialyzer bioincompatibility, protein energy wasting, long-term extracellular volume overload, and chronic infections. This is supported by the elevated serum levels of high-sensitivity C reactive protein (CRP) and other inflammatory cytokines (e.g., IL-1β, IL-6, and IL-18, tumor necrosis factor alpha, interferon gamma) in the dialysis population.

Among chronic infections, periodontitis is especially common among dialysis patients. It is a prevalent and persistent peripheral infection of gum tissue that is associated with poor oral health, smoking, and tooth loss and is caused by gram-negative anaerobic bacteria.

Dialysis patients also have increased circulating levels of endotoxin, which is linked to increased ultrafiltration volumes, suggesting that hemodynamic stress, liver blood flow redistribution, and gut ischemia may result in translocation of endotoxin from the gut into the bloodstream. Indeed directly observed changes in hepatic and intestinal perfusion during dialysis are associated with incremental increases in circulating endotoxin levels.

Diagnostics

Pulse-Wave Velocity

Pulse-wave velocity (PWV) is a measurement of arterial stiffness and is an independent predictor of cardiovascular risk. It can be assessed simply and noninvasively by measuring the carotid and femoral pulse pressures and the time delay between the two or by other methods relying on pulse-wave analysis. Direct measurement of aortic compliance is also possible by MRI. The value is affected by age, gender, and BP and should be adjusted for these factors. Studies in kidney failure patients have shown that along with age, pulse wave velocity is a potent predictor of cardiovascular and all-cause mortality.

Quantification of Vascular Calcification

The gold standard for measurement and quantification of vascular calcification is CT. This can be performed at several anatomical sites, such as the coronaries, abdominal aorta, and femoral arteries, and does not require the use of iodinated contrast. The Agatston score is one of the most commonly used quantitative scoring systems and has a strong correlation with clinical outcomes—patients who score higher have a significantly higher risk of mortality. CT could also, in theory, be used to monitor the progression of calcification and response to therapy. However, given the concerns about cumulative radiation exposure and the lack of an effective therapy that causes a regression of vascular calcification, routine quantification of vascular calcification by CT scanning is not currently widely recommended.

Diagnosis of Endothelial Dysfunction

The clinical diagnosis and quantification of endothelial dysfunction comprise three main possible options: in vivo functional tests, such as flow-mediated dilation (FMD); measurement of cellular or cell-derived endothelial biomarkers; and measurement of soluble biomarkers implicated in endothelial activation, such as clotting factors, adhesion molecules, and growth factors. These tests are still investigational and require proper validation in the clinical dialysis setting.

FMD is an ultrasound-based technique that tests the degree of brachial artery dilation after a standardized, transient period of locally induced ischemia-reperfusion stimulus. The vasodilatory response is mediated by endothelial nitric oxide release, and a reduced vasodilatory response after the ischemia-reperfusion stimulus is a marker of endothelial dysfunction. An impaired brachial artery vasodilatory response has been shown to be a powerful predictor of cardiovascular events in the general population. Impaired vasoreactivity has also been observed in kidney failure patients on HD compared to healthy controls and non-CKD patients, although its ability to predict clinical outcomes is at present unclear.

Among the endothelial cell-derived and cellular biomarkers, endothelial microparticles, circulating endothelial cells, and endothelial progenitor cells deserve to be mentioned. Endothelial microparticles and circulating endothelial cells are markers of endothelial activation and injury. They are elevated in conditions of hemodynamic stress and cardiovascular disease. Both these biomarkers are elevated in HD patients, especially in the setting of cardiovascular disease. Furthermore, preliminary evidence has shown a positive correlation between endothelial microparticle release and ultrafiltration rates with HD. On the other hand, endothelial progenitor cells reflect the endothelial ability to promote vascular repair and neoangiogenesis. Reduced circulating levels of endothelial progenitor cells have also been observed in CKD and dialysis patients. Overall, these biomarkers point out a pattern of endothelial dysfunction characterized by activation, injury, and impaired repair capacity.

Many soluble plasma and serum biomarkers of endothelial activation (e.g., Von Willebrand factor, tissue factor, thrombomodulin, adhesion molecules, vascular endothelial growth factor) have been found to be elevated in kidney failure patients; many of these factors are particularly elevated in kidney failure patients with protein-energy wasting, inflammation, and cardiovascular disease.

Treatment

The most important therapeutic approach to vascular disease in dialysis patients is preventive, by controlling both traditional and nontraditional risk factors.

Hypertension

The treatment of hypertension in relation to peripheral vascular disease follows the same recommendations as for the prevention of cardiovascular disease, presented earlier. It is worth noting that the same limitations we previously mentioned should be taken into account. Aggressive BP control, especially if attained with antihypertensive medications, is associated with intradialytic hypotension, orthostatic hypotension with higher risk of falling (e.g., due to cerebral hypoperfusion and facilitated by autonomic dysfunction), and vascular access thrombosis. Moreover, the use of beta-blockers for the treatment of hypertension should also be carefully considered in HD patients because of the risk of bradyarrhythmias (as shown by the interesting results of the recent Monitoring in Dialysis study). In conclusion, the lack of established BP targets in the kidney failure population and the multitude of potential complications associated with antihypertensive medications warrant special care in the treatment of hypertension.

Vascular Calcification

At present, the principal therapeutic approach to limiting the progression of vascular calcification has been careful management of the calcium-phosphate balance, which comprises vitamin D supplementation, dietary phosphate restriction, prescription of calcium-free phosphate binders, optimization of dialysis therapy with reduced calcium supplementation, and extended treatment times to optimize dialytic phosphate removal. This approach, however, has several limitations.

First, there is no consensus on the optimal target serum phosphate levels to be achieved. Second, there is evidence of a benefit on clinical outcomes for the calcium-free phosphate binder sevelamer over calcium carbonate (while also showing vascular calcification regression on CT coronary artery calcium scores); there is insufficient evidence to recommend against the use of calcium-based phosphate binders. Third, there is no evidence showing clinical benefit from better dialysis-based phosphate removal other than on serum phosphate levels and phosphate binder use.

Additional treatment options are currently being explored. In particular, magnesium supplementation, either by oral supplements or by increasing dialysate magnesium, has also been recently shown promise in reducing vascular calcification progression in maintenance HD patients. Sodium thiosulfate, currently used for the treatment of calciphylaxis, has also been shown to revert progression of vascular calcification in HD patients.

Enhancing Uremic Toxin Management

Online hemodiafiltration and, more recently, expanded HD (using mid cutoff range dialyzers) have shown promise in increasing the spectrum of uremic toxin removal, either by exploiting both diffusive and convective removal (hemodiafiltration) or by employing dialyzers, with increased and more regular pore size (expanded HD). Both these techniques have shown preliminary evidence of higher clearance of uremic toxins (middle molecules in particular) associated with inflammation, oxidative stress, and endothelial dysfunction. Preliminary evidence also showed improvement in endothelial function measured with flow-mediated dilatation in online hemodiafiltration versus standard HD. However, several randomized controlled trials of thrice-weekly high-volume online hemodiafiltration failed to show a clear advantage in clinical outcomes over standard HD. Although post hoc analysis looking at subgroups with higher achieved convective volumes showed a survival benefit over subgroups with lower achieved convective volumes, the clinical evidence in favor of online hemodiafiltration remains overall inconclusive and may be biased by differences in baseline patient characteristics and unexplored consequences (e.g., better performing vascular access and higher degree of cooling in patients receiving higher convective volumes). Additionally, in a randomized crossover trial, online hemodiafiltration failed to show any benefit on hemodynamic stability, myocardial perfusion, and systolic function compared to standard HD. The benefits of expanded HD on clinical outcomes remain yet to be proven, although they may be closely linked to a superior uremic toxin clearance profile compared to standard techniques.

Increasing treatment times and frequency has shown benefits on circulating endotoxin levels; frequent dialysis schedules, such as short daily and nocturnal HD, have been associated with lower circulating endotoxin levels, likely due to lower ultrafiltration rates with a better hemodynamic tolerability of these treatments, resulting in a lower endotoxin translocation from the gut. Other emerging approaches to reduce uremic toxins levels include administering oral adsorbents (e.g., AST-120) and interventions to manipulate the gut microbiota (e.g., prebiotics, probiotics, fecal transplant).

Other Critical Organ Systems Requiring Protection

The cardiovascular risk associated with HD is the result of the combination of several predisposing factors and repetitive episodes of HD-induced ischemic injury. Although the evidence of cardiovascular toxicity associated with standard HD regimens is now accepted, recent evidence has also shown that other end-organs may be as susceptible, such as the kidneys, the brain, and the liver–gut axis. In particular, repetitive hemodynamic instability results in an accelerated decline in residual kidney function, cognitive function and escalates the circulating endotoxin load, likely impacting quality of life and survival.

The Liver–Gut Axis and Circulating Endotoxins

Ultrafiltration has also been associated with a fall in splanchnic perfusion. This causes ischemic injury to the gut

mucosa and, along with mucosal congestion due to extracellular volume overload, impairs the gut barrier and leads to massive endotoxin translocation from the lumen into the portal circulation. This results in a far higher endotoxin load compared with kidney failure patients on conservative treatment. In order to reach the systemic circulation, the endotoxin load from the guts must be associated with an impaired liver-detoxifying function. Indeed, the liver plays an essential role as a barrier to bacterial fragments and endotoxin, as well as detoxification from uremic toxins. However, the effects of HD on liver perfusion are less clear and have only recently been investigated. Because of its dual blood supply, the liver is resilient to a transient reduction in total hepatic blood flow. To maintain its perfusion, changes in hepatic arterial blood flow occur to compensate for changes in portal blood flow—the "hepatic arterial buffer response." During HD, one study has observed a reduction in total hepatic blood flow by indocyanine green clearance. This provides preliminary evidence of intradialytic hepatic dysfunction, although whether the reduction in total blood flow is the result of reduced arterial and/or portal blood flow is currently unclear. An acute, intradialytic alteration of hepatic function associated with increased portal endotoxin and uremic toxin load then results in increased toxin delivery in the systemic circulation.

The evidence so far available suggests a key role of the liver–gut axis in the regulation of uremic toxin and endotoxin load. However, more studies are necessary to ascertain the pathophysiology of intradialytic liver dysfunction, understand its clinical significance, and explore the efficacy of targeted interventions.

Vascular Brain Injury

Abnormalities of cognitive function and high incidence of depression are characteristic of HD patients. Although previously attributed to the humoral effects of uremia, it is becoming appreciated that many elements of the overall disease state in CKD patients increasingly contribute to functional disturbances and physical brain injury. These factors range from those associated with the underlying primary diseases (cardiovascular disease, diabetes, etc.) to those specifically associated with the requirement for dialysis (including consequences of the HD process itself). They are, however, predominantly ischemic threats to the integrity of brain tissue.

There are multiple pathologies that have been described by brain MRI appearances in dialysis patients. These may be entirely asymptomatic or linked to more subtle defects in neurocognitive function, often only apparent on specific testing. Many of the same processes drive this entire spectrum and are often progressive. These abnormalities range from classic stroke to silent cerebral infarct and more subtle changes both in the white matter (leukoaraiosis) and gray matter (cortical atrophy). In this way, the situation with cardiac injury on dialysis is mirrored—with more non-ST segment elevation MI than classical transmural MIs.

Leukoaraiosis is the rarefaction of the brain white matter caused by loss of axons and myelin due to ischemic injury and appears to be of central importance in the neurocognitive defects associated with HD. MRI appearance of this entity is that of high signal intensity on T2-weighted images. Leukoaraiosis has been described as a risk factor for developing dementia, mobility problems, and strokes.

Recently, more advanced brain imaging (diffusion tensor imaging [DTI]) has demonstrated it to be a universal finding in HD patients after only 3 months of dialysis. The severity of reduction in cognitive function was proportional to the distribution and amount of white matter injury, and in turn, this was proportional to the degree of cardiovascular instability during HD sessions. This further reinforces the central role that dialysis treatment might play in the development of functionally significant brain injury.

Direct evidence has recently been published relating to the direct link between hemodynamic tolerability of dialysis and brain injury as measured by brain DTI MRI to quantify and localize white matter ultrastructural injury. HD is associated with progressive further ultrastructural white matter injury, and this has the signal signature pathognomonic of vascular injury. The improvement of hemodynamic tolerability using individualized cooling of dialysate entirely abrogated this progressive injury in a recent pilot randomized controlled trial, strongly supporting the integral role that the HD process itself plays in the evolution of brain injury in HD patients.

Kidney and Residual Renal Function

Residual kidney function is an important factor associated with better survival in dialysis patients. It has been observed that residual kidney function declines more rapidly in HD patients than in those untreated by dialysis or maintained with peritoneal dialysis. Analogously to what occurs for intradialytic myocardial blood flow, a recent perfusion CT-based study has shown a significant acute fall in kidney blood flow during HD. This study may provide the pathophysiological evidence to explain the accelerated decline in residual kidney function that has been observed in HD patients; repetitive, acute, transient episodes of intradialytic kidney blood flow reduction ("kidney stunning") may be translated into cumulative acute kidney injury episodes. Yet again, strategies to improve hemodynamic stability and/or systemic resilience to ischemia-reperfusion injury may help in preserving residual kidney function and improve HD patients' long-term prognosis.

Conclusion

Because of the unique collection of pathophysiological processes that are at work in dialysis patients, the therapeutic approach needs to be substantially different from the one applied to the general population and CKD patients not on dialysis. More specifically, the optimization of dialysis

therapy and the adaptation of therapeutic protocols approved for the general population may be of central importance. Much of this appreciation is a still matter of ongoing discovery and controversy. The lack of robust clinical evidence and the necessity for testing novel viable therapeutic options combine the therapeutic frustration for clinicians with the exciting prospects of real progress in addressing the most common causes of excess mortality in dialysis patients.

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Management of Dyslipidemia in Long-Term Dialysis Patients

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Introduction

Dyslipidemia is commonly observed in adults treated with hemodialysis (HD) and peritoneal dialysis (PD). The most prevalent pattern is increased plasma triglyceride concentrations (linked to an accumulation of triglyceride-enriched apolipoprotein-B particles) and decreased plasma concentrations of high-density lipoprotein (HDL). In addition, PD patients usually have increased low-density lipoprotein (LDL) concentrations. Atherogenic changes in the composition of lipoproteins have also been documented in HD and PD patients. Dialysis patients experience grossly elevated risks of cardiovascular events and mortality. Accordingly, evidence of the benefits and harms of lipid management on cardiovascular risk in the setting of dialysis is of central importance to clinical practice.

In contrast to the general population and adults with cardiovascular disease, lipid abnormalities inversely correlate with cardiovascular disease and all-cause mortality in observational studies among HD and PD patients. Notably, higher levels of serum total and LDL cholesterol are associated with lower risks of total and cardiovascular death, which may in part be explained by effect modification from systemic inflammation and/or malnutrition, which are independently associated with poor outcomes.

Uncertainty about the effects of lipid-lowering treatment in end-stage kidney disease (ESKD) patients has occurred due to differing conclusions among large, randomized trials of statin therapy with or without ezetimibe. Numerous randomized controlled trials evaluating lipid management in the dialysis setting are available. This chapter examines existing data for treatment effects of lipid management among ESKD.

Diet and Exercise

Trials evaluating the effects of dietary or lifestyle management of dyslipidemia among ESKD patients are sparse, and there can be very low confidence in the effectiveness of dietary and lifestyle modifications on clinical outcomes, including serum cholesterol levels and cardiovascular events among HD and PD patients. Most existing randomized trials evaluate the effects of dietary management in predialysis patients. In observational studies, there is evidence that dietitian care for more than 12 months before dialysis therapy initiation has an independent association with lower cholesterol levels and lower mortality in the first year of dialysis treatment. A large prospective cohort study of over 8000 participants treated with HD suggests an association between higher consumption of fruits and vegetables (two to three servings per day) and lower all-cause mortality. However, the effects on adverse events such as hyperkalemia were not available, and findings need to be confirmed in randomized controlled trials.

In a systematic review of randomized trials of regular exercise training (lasting 8 weeks or longer) among adults with chronic kidney disease, treatment effects on serum lipid levels were not known, although exercise training improved aerobic capacity, muscle, and cardiovascular function, walking capacity, and health-related quality of life. In a randomized controlled study comparing exercise with no specific training over 12 months among 25 HD patients, training lowered triglyceride levels and increased plasma HDL cholesterol levels, while there was no change in total and LDL cholesterol concentrations. However, until randomized trials of dietary interventions and exercise are conducted to examine treatment effects on patient-level outcomes, such as cardiovascular risk, the benefits of exercise appear limited to improved quality of life, functional capacity, and specific dietary management recommendations are not possible. This is despite ESKD patients, caregivers, and clinicians considering heart health promotion as a key treatment uncertainty in the setting of dialysis.

Lipid-Lowering Drugs

Several randomized controlled trials of lipid-lowering therapy in HD and PD patients are now available and provide

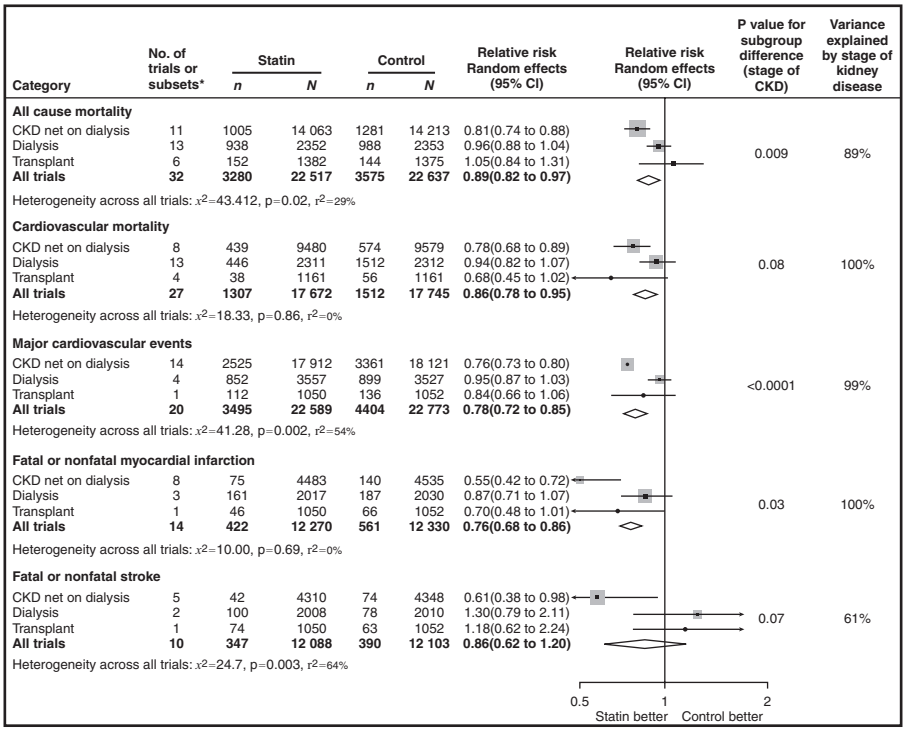
moderate to high-quality evidence for the effects of treatment on mortality and cardiovascular events. Data for the effects of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) used with or without ezetimibe are available for 7982 HD and PD patients.

Despite clinically important reductions in serum levels of total cholesterol (–47.5 mg/dL [–1.2 mmol/L]), LDL cholesterol (–43.1 mg/dL [1.1 mmol/L]), and triglycerides (–21.9 mg/dL [–0.2 mmol/L]) during treatment lasting 6 months on average, statin therapy had little or no effect on all-cause mortality (relative risk [RR], 0.96; 95% confidence interval [CI], 0.88 to 1.04), cardiovascular mortality (RR, 0.94; 95% CI, 0.82 to 1.07), and major cardiovascular events (RR, 0.95; 95% CI, 0.87 to 1.03) (Fig. 48.1). Similarly, statin therapy had uncertain effects on risks of myocardial infarction (RR, 0.87. 95% CI, 0.71 to 1.07) and stroke (RR, 1.30; 95% CI, 0.79 to 2.11). The effects of treatment were predominantly examined in HD patients; information about treatment effects and safety of statins in PD patients is currently insufficient to make treatment recommendations. Overall, clinicians may reasonably choose not to initiate statin therapy in ESKD patients. In fact, the lack of clinical effect of lipid-lowering strategies on cardiovascular risk despite clinically important reductions in cholesterol and triglyceride levels in PD and HD patients suggests that pharmacologic treatment to target specific lipid levels is ineffective in long-term dialysis settings.

In a meta-analysis of randomized controlled trials of fibrate therapy among 16,869 adults with or at risk of chronic kidney disease, fibrates decreased total cholesterol (–12.4 mg/dL [–0.32 mmol/L]) and triglyceride (49.6 mg/dL [–0.56 mmol/L]) levels, increased HDL levels (2.31 mg/dL [0.06 mmol/L]), and had nonsignificant effects on LDL cholesterol. No information was available about fibrate treatment among HD or PD patients.

Other drugs with effects on lipid profiles in ESKD patients have not been shown to have effects on patient-level outcomes, while safety data are sparse. These drugs include bile acid sequestrants, niacin, acipimox, pantetheine, and probucol, which are not recommended for use in PD or HD patients.

Several possible explanations have been advanced to explain the smaller clinical effects of lipid-lowering treatment among ESKD patients compared with the consistent proportional reductions in cardiovascular events among people with or at risk of cardiovascular disease and who have normal kidney function or mild to moderate kidney disease in whom a proportional risk reduction in major cardiovascular events of 20% for every 40 mg/dL (1 mmol/L) reduction in LDL cholesterol is observed. The pathologic etiology of cardiovascular disease in HD and PD patients is dominated by vascular calcification, cardiac hypertrophy, and arterial stiffening, which are biological processes that might be less amenable to the beneficial effects of lipid reduction with statin or fibrate therapy.



Effect of statin therapy versus placebo or no treatment control on total and cardiovascular mortality and major cardiovascular events grouped by stage of chronic kidney disease. 95% CI, 95% confidence interval; CKD, chronic kidney disease. *Subsets of trials refers to presence of data from subgroups with chronic kidney disease not on dialysis or cohorts on various types of dialysis (peritoneal dialysis or hemodialysis) within broader trials

• **Fig. 48.1** Effect of statin therapy versus placebo or no treatment on total and cardiovascular mortality and major cardiovascular events. (From Palmer SC, Craig JC, Navaneethan SD, et al. Benefits and harms of statin therapy for persons with chronic kidney disease. *Ann Intern Med.* 2012;157:263–275 [figure, p 267].)

The existing evidence evaluating statin therapy in ESKD patients is high to moderate quality, indicating that additional trials of statin management in HD and PD patients are unlikely to change our confidence in the results. Based on existing evidence, there is little to support a recommendation for pharmacologic treatment of lipid abnormalities among HD and PD patients.

Other Lipid-Lowering Strategies

Fish oil supplements (0.9–3.0 g/day) reduce serum triglycerides (–20.4 mg/dL [0.23 mmol]) and total cholesterol (–4.63 mg/dL [0.12 mmol/L] levels and increase HDL cholesterol (7.7 mg/dL [0.20 mml/L]) levels among HD and PD patients. A systematic review of randomized controlled studies suggests that fish oil supplementation may decrease cardiovascular mortality in participants treated with HD (seven trials; 1045 participants; 39 events; RR, 0.45, 95% CI, 0.23 to 0.89). However, the certainty of evidence was low and longer-term, well-powered trials are needed to assess the benefits and harms of fish oil therapy in this population. A large international trial is ongoing to assess the effect of fish oil supplementation on major fatal and nonfatal cardiovascular events in up to 5000 HD patients. In one study, short-term treatment with adrenocorticotrophic hormone (ACTH) was effective in reducing the concentrations of LDL cholesterol—as well as those of lipoprotein (a)—in HD patients.

Treatment with sevelamer hydrochloride, which is a non-aluminum- and non-calcium-containing polymer, reduces serum phosphorus and LDL cholesterol in HD patients. These simultaneous effects make it a candidate drug for reducing the risk of CVD in HD patients. However, a clear demonstration of the superiority of any specific class of phosphate binder, including sevelamer, lanthanum, colestilan, bixalomer, and iron-containing compounds, on mortality and cardiovascular risk among ESKD patients is not yet available. L-Carnitine is an essential cofactor for fatty acid transport into mitochondria for oxidation. Of all forms of renal replacement therapy, only HD is associated with free carnitine deficiency. In a meta-analysis of 49 randomized controlled trials of L-carnitine supplementation among 1734 HD patients, L-carnitine significantly reduced serum LDL cholesterol (–5.82 mg/dL [–0.15 mmol/L]) but had no effect on total cholesterol, HDL cholesterol, or triglycerides. The treatment effects of L-carnitine on mortality and cardiovascular events remain uncertain. Systemic heparinization that is used routinely in HD might adversely affect plasma lipids through the depletion of lipoprotein lipase, leading to the accumulation of triglyceride-enriched apolipoprotein-B particles. Low-molecular-weight heparin preparations are expected to have a favorable effect on lipid metabolism because only fractions of high-molecular-weight heparin preparations account for lipolytic effects; however, a recent systematic review has reported conflicting effects of heparin formulations on lipid levels in HD patients. Reasons for these conflicting results potentially include differences among preparations and modes of administration of low-molecular-weight heparin preparations.

To date, attempts to improve lipid profiles by altering dialysate composition in HD have been largely unsuccessful. Moreover, studies examining the effects on serum lipids of different glucose-free dialysate fluids in PD patients are inconclusive. Modest reductions in total cholesterol have been observed after the substitution of glucose by amino acid fluids in PD patients. The use of high-molecular-weight glucose polymer-based solution led to a nonsignificant 6%–10% reduction in cholesterol and triglyceride levels over a 6-month period. Randomized trials have found that high-flux dialysis membranes have little or no effect on lipid profiles in HD patients.

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End-Stage Kidney Failure in the Diabetic Patient

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Introduction: The Diabetic End-Stage Kidney Disease Population

The prevalence of diabetes continues to increase in both developed and developing countries. End-stage kidney disease (ESKD) is the most recognizable result of diabetic chronic kidney disease (CKD). Patients with diabetes mellitus are at increased risk of ESKD. Diabetes mellitus continues to be a worldwide epidemic, and with it, diabetic CKD remains the single most important cause of ESKD. According to both incidence and prevalence trends, although the incidence of diabetic ESKD has stabilized, the prevalence continues to increase. The cause of ESKD may be diabetes, or the patient may have diabetes as a comorbidity. While sentinel diabetes-related complications overall have declined over time, the rates of ESKD have decreased less than rates of other complications. Although data indicate that the relative risk for ESKD due to diabetes, compared to the risk in the nondiabetic population, has fallen by half, that relative risk remains over 6. The most recent U.S. Renal Data System (USRDS) data trends for the ESKD population are shown in Table 49.1. (In total, diabetes is present in about 60% of all U.S. dialysis patients.) USRDS prevalence numbers for years 2015–2017 in the general population rose slightly with 35% attributed to diabetes; for incidence numbers in the same years, 46% were related to diabetes. Worldwide analysis of crude incidence rates indicates a broad range of rates due to diabetic ESKD compared to the general population (Fig. 49.1). Although the lifetime risk of ESKD for patients with type 1 diabetes is 10%–15%, it appears to vary in study cohorts in different countries. The incidence of ESKD due to diabetes overall is higher in males (particularly in the white population) with increasing age, and significantly higher in Black-Americans, Hispanics, Asians, and Alaskan natives, compared to whites. In the United States, reductions by half in ESKD rates over 20 years in Native Americans, who have the highest rates of diagnosed diabetes, have been attributed to improvements in clinical care. Incidence rates appear to vary over fourfold among geographic areas in the United States. It is now understood that ESKD increases the morbidity of diabetes mellitus markedly; kidney disease accounts for most of the excessive cardiovascular and all-cause mortality risk associated with diabetes. Regarding dialytic management, those with ESKD attributed to diabetes are more likely to be treated with in-center hemodialysis (HD) and less likely to have a transplant. This chapter emphasizes these and other features of special importance to the adult ESKD population with diabetes mellitus.

Predialysis Care/Dialysis Initiation

Patients with diabetic CKD may develop symptoms such as gastroparesis or neuropathy, which mimic those of uremia; may be prone to malnutrition, hyperkalemia, or volume overload; or may develop uremic symptoms earlier than those without diabetes. A recent study addressed the value (hospitalization, mortality risks) of primary care physician continuity before and during the transition from CKD to maintenance dialysis. High PCP continuity was associated with a reduction in hospitalizations for patients with diabetes. Conventional wisdom has been that ESKD patients with diabetes require earlier initiation of dialysis than nondiabetics, a "preventive" strategy to slow progression of some complications of diabetes and to improve outcomes. While the trend toward early dialysis starts in the general ESKD population reversed over a decade ago, diabetic patients have continued to be among patients in whom dialysis is initiated early. Diabetes strongly predicted the early start of dialysis according to recent USRDS data reports, although the difference in eGFR at initiation was slight. Relative to other outcomes data, information concerning mortality rates and factors that influence mortality soon after initiation in incident dialysis patients is limited. Mortality risk among HD patients is highest in the first 3 to 4 months after dialysis initiation. Data on risk/benefit of early initiation in patients with diabetes, however, show mixed results. A systematic review in 2016 indicated that the effect of timing of initiation of dialysis did not differ between patients with and without diabetes.

TABLE 49.1 Recent Incidence and Prevalence (Numbers of Patients) of ESKD Attributed to Diabetes

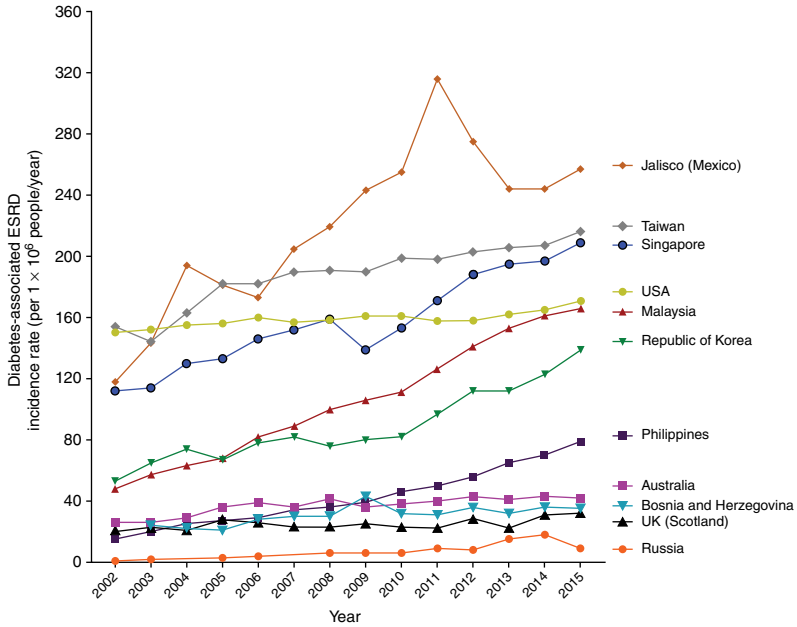
	2015	2016	2017
Incident Patients			
Diabetes	56,219	57,721	57,715
All	125,237	125,408	124,500
% Diabetes	45	46	46
Prevalent Patients			
Diabetes	262,292	274,885	282,686
All	766,178	789,165	808,159
% Diabetes	34	35	35

ESKD, End-stage kidney disease.
From United States Renal Data Systems. 2019 USRDS Annual Data Report. Epidemiology of Kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; 2019.

Dysglycemia

Patients with either type 1 or type 2 diabetes and CKD/ESKD require more comprehensive laboratory monitoring, such as glucose levels and hemoglobin A_{1c} (HbA_{1c}) testing. The maintenance of glucose homeostasis is affected both by diabetes and kidney failure. The core pathologic defects in diabetes are decreased insulin secretion (type 1 diabetes) and insulin resistance, impaired insulin secretion, increased hepatic glucose production, decreased glucose uptake by muscle, and increased renal glucose reabsorption (type 2 diabetes). When kidney impairment progresses additional alterations occur, which may further cause dysglycemia; insulin secretion by the pancreas is reduced, and insulin clearance is diminished. With a molecular weight of about 6000 daltons, insulin has a high renal clearance through filtration and secretion. Renal insulin clearance is reduced as GFR falls to 15–20 mL/min/1.73 m^2. Abnormal glucose homeostasis is further affected in uremic individuals by peripheral insulin resistance, involving defective glucose uptake and reduced muscle protein anabolism (but not cellular potassium uptake). Glucose uptake mediated by specific transporter proteins is a major action of insulin. Insulin resistance in CKD is a unique metabolic abnormality induced by factors such as uremic toxins, chronic inflammation, excess visceral fat, oxidative stress, metabolic acidosis, and deficiency of vitamin D and erythropoietin. However, the health implications of insulin resistance have not been adequately evaluated in the ESKD population. Improvement in insulin resistance with dialysis treatment is due at least in part to removal of uremic toxins. To what extent insulin resistance also contributes to protein-energy wasting through the ubiquitin-proteosome pathway to atherosclerosis and cardiovascular disease remains undetermined in ESKD patients.

The net clinical effect of these various defects in a given diabetic ESKD patient is variable; insulin resistance in advancing CKD may be offset by insulin retention and poor caloric intake; improvement in insulin resistance by dialysis may be offset by more robust caloric intake as uremia improves. A significant reduction in insulin requirements during and following an HD treatment may be anticipated. While clinical assessment of insulin resistance in diabetic ESKD is not practical, it remains a potential therapeutic target. However, insulin sensitizers, a potential treatment aimed at insulin resistance, are either sparingly used or contraindicated in ESKD.



• **Fig. 49.1** Trends in the incidence rate (per million people in the general population/year) of diabetes-related ESRD, by country, between 2002 and 2015. *ESRD*, End-stage renal disease. (From Harding JL, Pavkov ME, Magliano DJ et al. Global trends in diabetes complications: a review of current evidence. *Diabetologia.* 2019;62:3–16.)

Prediabetes

In recent years, there has been a marked increase in the number of U.S. adults with prediabetes to at least 35% of the general population. Prediabetes is conventionally identified by an HbA_{1c} value of 5.7%–6.4%. The risk of overt diabetes developing is not linear but increases with higher HbA_{1c} levels below the diabetic range. Prediabetes is associated with increased risk of all-cause and cardiovascular mortality in the general population. ESKD patients who test in the prediabetic range should have annual monitoring for the development of diabetes, lifestyle interventions, and identification/treatment of other cardiovascular risk factors, such as hypertension, hyperlipidemia, and obesity. Limited data suggest that having ESKD may be associated with a lower risk of the development of incident diabetes, although the confounding effects related to ESKD and lower HbA_{1c} levels described later need to be taken into account.

Assessing Glycemic Control in End-Stage Kidney Disease

Providing ESKD management for patients with diabetes mellitus requires awareness of how glycemic control is being assessed. The two conventional techniques available for assessing the effectiveness of glycemic management are self-monitoring of blood glucose and HbA_{1c}. Proposed glycemic control parameters for diabetic ESKD patients are fasting blood glucose of 100–140mg/dL and 2-hour postprandial blood glucose of <200mg%. In the general diabetes population, landmark studies have established HbA_{1c} as the primary predictor of diabetic complications. Among ESKD patients, however, the limitations of HbA_{1c} have more recently become well recognized. HbA_{1c} reflects average blood glucose concentrations over approximately the three preceding months, has some correlation with blood glucose levels, and has provided evidence in interventional trials of the benefit of tight glycemic control. It does not inform about glycemic variability or hypoglycemia. However, reliance on HbA_{1c} in a given individual is limited by the fact that HbA_{1c} values may be widespread when plotted against average glucose levels. Current society guidelines continue to recommend an HbA_{1c} target of $<7.0\%$ in the general population, with the caveat that goals must be individualized based on factors such as duration of diabetes, age and life expectancy, and comorbid conditions.

However, it should be noted that extensive trials have forced a reevaluation of the validity of the HbA_{1c} test in the setting of ESKD, as well as indicating only a weak correlation between the test and outcomes in this population. The major source of uncertainty regarding the role of HbA_{1c}-based glycemic control in ESKD at this time is the unreliability of the HbA_{1c} test itself. Compared to the general diabetic population, correlation with average glucose levels is weaker. Data indicate that HbA_{1c} measurements may be misleadingly low in patients with ESKD, resulting in an underestimation of the degree of hyperglycemia. The most likely sources of discordance from other glycemic tests in kidney patients are anemia, the use of erythrocyte stimulating agents (ESAs), and the administration of intravenous iron. ESAs stimulate the production and release of immature erythrocytes, whose hemoglobin appears to have reduced glycosylation. Although comparative data are limited, HbA_{1c} values in the setting of ESKD, as a rough estimate, generally measure about 1% lower than expected for given levels of serum glucose during the time preceding the HbA_{1c} test.

In recent years, increasing consideration has been given to glycated albumin (GA) as a replacement for HbA_{1c} for assessing glycemic control in ESKD patients. GA reflects glucose exposure for only the previous 2 weeks and requires more frequent testing. Unlike with HbA_{1c}, there is no international standardization of the GA measurement. However, GA results are not confounded by the presence of anemia or the use of ESAs. Limited data suggest good correlation with values obtained by continuous glucose monitoring (CGM).

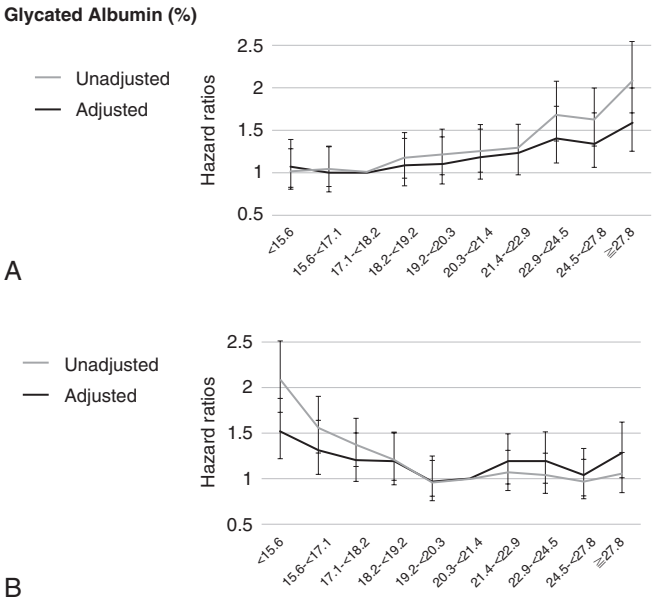
Achieving Glycemic Control in End-Stage Kidney Disease

Treatment goals for patients with advanced CKD, at least for those with related limited life expectancy and at risk for hypoglycemia, have been extended in recent years to above 7%. However, there have been no randomized, interventional clinical trials to evaluate the beneficial effects of glycemic control in patients with diabetes and ESKD. Two frequently cited, comparably sized retrospective observational studies with methodological differences have reported on the relationship of glycemic control and outcomes in ESKD patients with diabetes, yielding somewhat conflicting conclusions. Kalantar-Zadeh et al. demonstrated, after adjustment for multiple potential confounders, an incremental relationship between higher HbA_{1c} values and higher mortality. A follow-up study by the same investigators indicated that poor glycemic control ($HbA_{1c} \geq 8.0\%$) was associated with high all-cause and cardiovascular deaths. Williams et al. were able to establish only a weak and variable relation, and only when follow-up was extended to a maximum of 3 years. Findings from the Dialysis Outcomes and Practice Patterns Study (DOPPS) indicated that mortality increased as HbA_{1c} exceeded the 7%–7.9% range. A meta-analysis of nine observational studies and one secondary analysis indicated that a higher mortality risk did not occur until the HbA_{1c} levels were $\geq 8.5\%$. Patients with very low HbA_{1c} levels are also at risk (Table 49.2). In a post hoc analysis of the German Diabetes and Dialysis Study (4D Study), each 1% increase in baseline HbA_{1c} was associated with an 18% higher risk of sudden cardiac death, although myocardial infarction events were not affected. Overall, these data suggest that HbA_{1c} ranges of 7%–8% may be optimal. The Kidney Disease Outcome Quality Initiative (KDOQI) Clinical Practice Guidelines based on

TABLE 49.2 Glycated Hemoglobin Levels and Mortality Risk (Adjusted) for Prevalent Patients With Diabetes Treated With Hemodialysis

HbA_{1c} (%)	Pooled HR (95% CI)	P
Baseline		
≤5.4	1.16 (0.79-1.70)	0.5
5.5-6.4	1.04 (0.78-1.37)	0.8
6.5-7.4	1.00 (reference)	-
7.5-8.4	1.08 (1.01-1.15)	0.03
≥8.5	1.20 (1.01-1.42)	0.04
Mean		
≤5.4	1.06 (0.87-1.28)	0.4
5.5-6.4	0.92 (0.83-1.03)	0.2
6.5-7.4	1.00 (reference)	-
7.5-8.4	1.03 (0.91-1.16)	0.4
≥8.5	1.31 (1.12-1.52)	<0.001

Adjusted for age, sex, diabetes type, dialysis vintage, and hemoglobin concentration when available.
HR, Hazard ratio.
From Hill CJ, Maxwell AP, Cardwell CR, et al. Glycated hemoglobin and risk of death in diabetic patients treated with hemodialysis: a meta-analysis. *Am J Kidney Dis.* 2013;63:84–94.



• **Fig. 49.2** All-cause mortality (hazard ratios) according to deciles of glycated albumin (A) and hemoglobin A1c levels (B). Adjusted variables included age, sex, modality, vintage, body mass index, smoking, type of diabetes, hypertensive agents, diabetes treatment, hemoglobin, albumin, Kt/V, and other factors. (From Hoshino J, Hamano T, Abe M, et al. Glycated albumin versus hemoglobin A1c and mortality in diabetic hemodialysis patients: a cohort study. *Nephrol Dial Transplant.* 2018;33:1150–1158.)

observational studies suggest a higher ESKD mortality risk with HbA_{1c} levels <6.5 and $>8.0\%$. However, a report on DOPPS participants from Japan demonstrated that optimal HbA_{1c} levels may vary among countries; the association of HbA_{1c} levels and mortality was U shaped, but the HbA_{1c} level associated with the lowest mortality in diabetic HD patients in Japan (6.0%–7.0%) differed from that of the United States.

Although not as well studied, GA has been proposed as a superior alternative to HbA_{1c} for determining the value of glycemic control in ESKD patients with diabetes. Clinical practice guidelines for diabetes do not recommend GA as the first-line metric of glycemic control. Its linkage to average glucose levels and prognostic significance is less well established in ESKD. GA has been shown to accurately predict the risk of hospitalization and death in patients with diabetes on HD and, with less evidence, in those on peritoneal dialysis (PD). In a recent analysis of samples from the German 4-D study, a high risk of mortality in the highest quartile of baseline GA was demonstrated. Comparative HbA_{1c} and GA data from a recent 1-year mortality outcomes study from Japan are shown in Fig. 49.2.

Guideline recommendations indicate that the intensity of glycemic control must be individualized based on potential risks and benefits. An HbA_{1c} target using the HbA1c metric of closer to 7% for younger, incident ESKD patients is recommended, and a target closer to 8% for longstanding diabetics, older patients, longer dialysis vintage, or those with multiple comorbid conditions. For real-time assessment, CGM profiling is increasingly valued, particularly given the potential effects of the dialysis treatment on short-term glycemia. Increased glycemic variability, a possible cardiac risk factor, has been demonstrated on dialysis days and reduced insulin requirements the day after dialysis. In a recent report, closed-loop insulin delivery provided safe and effective diabetes control for in-patients on HD. Patients managed with a subcutaneous insulin pump coupled with a continuous glucose monitor by means of a computer algorithm spent almost 40% more time in the glucose target range than the control group.

Diabetic Ketoacidosis/Hyperosmolar Coma

Potentially lethal hyperglycemic crises such as diabetic ketoacidosis (DKA) and hyperosmolar coma occur infrequently in ESKD patients with diabetes but may be severe and prolonged when they do occur. DKA is a complex disorder that affects volume status, electrolytes, and acid-base balance. It usually affects patients with type 1 diabetes and rarely those with new-onset type 2 diabetes. The underlying pathophysiology is that of absolute or relative insulin deficiency, insulin resistance, and increased counter-regulatory hormones. Common precipitating causes are omission of insulin doses, myocardial ischemia or infarction, and infection. Making the appropriate diagnosis in the ESKD patient is based on hyperglycemia, positive serum ketones, metabolic acidemia, and an increased anion gap. However, one caveat is that the diagnosis may be delayed insofar as the degree of hyperglycemia may be mild, the plasma reaction for ketones may be negative, and the anion gap may not be affected. The diagnosis may also be delayed because the clinical presentation itself of severe hyperglycemia and ketoacidosis is atypical in patients with

ESKD. Because osmotic diuresis does not occur, volume contraction is avoided (unless vomiting, diarrhea, and excessive insensible loss simultaneously occur). Patients may present with weight gain, thirst, pulmonary congestion, and in extreme circumstances, coma. However, because the rise in serum osmolality and sodium levels are not marked, there may be few neurologic symptoms. The total body potassium deficit, typically significant in non-ESKD DKA, is limited, and hyperkalemia may result. Because excessive urinary phosphate excretion does not occur, hypophosphatemia is not expected. Magnesium deficiency is absent. The bicarbonate deficit may be variable.

It follows that the acute management of DKA/hyperosmolar coma should be modified in ESKD patients. Insulin, frequently in low doses, is the only treatment required in many cases. Hypoglycemia should be avoided. (Current guidelines for treatment of DKA, in general, recommend against the use of bolus doses of insulin. Aggressive insulin treatment may result in severe and prolonged hypoglycemia.) Administration of large volumes of crystalloid is inappropriate, as patients have not had characteristic losses and are already at risk for volume overload. Intravenous crystalloid requirement may be increased if gastrointestinal (GI) losses have occurred. The use of parenteral bicarbonate is not indicated unless the level is critically low, particularly as it may exacerbate volume overload. No phosphate replacement is generally needed. Typical indications for urgent dialysis include pulmonary edema and hyperkalemia. While the patient is being stabilized, a cause for the episode of DKA/hyperosmolar coma should be urgently pursued.

Hypoglycemia

In recent years, there has been renewed concern regarding hypoglycemia as a determinant of adverse clinical outcomes in ESKD. Patients with ESKD, regardless of diabetes status, are prone to hypoglycemia, sometimes spontaneous, and sometimes related to hyperglycemia treatment. Likewise, among patients with hypoglycemia, ESKD is a common comorbid condition. Patients with both diabetes and ESKD are at particularly high risk of hypoglycemia, which adds to the case for avoiding intense glycemic control in this population. A recent study used International Classification of Diseases, Ninth Revision (ICD-9) codes to identify admissions for hypoglycemia as the primary admitting diagnosis, with and without ESKD, in a nationwide U.S. cohort. Almost 12% had ESKD, with higher rates in Black-Americans and Hispanics. Hypoglycemic patients with ESKD had higher hospitalization costs, longer lengths of hospital stay, and a threefold higher mortality.

The cause of hypoglycemia in ESKD patients is frequently multifactorial. Declining kidney function leads to reduced renal insulin clearance, and degradation of insulin in peripheral tissues is also decreased. In addition, defenses against hypoglycemia are not intact; renal gluconeogenesis, a protective source of glucose production from precursor molecules during starvation, is impaired. Patients with ESKD may also have diminished glycogen stores due to suboptimal nutrition.

As antidiabetic agents are likely contributors, evaluation should include assessment of the glycemic regimen and nutritional status leading up to the hypoglycemic event. In addition, causes of hypoglycemia found in the absence of diabetes or ESKD, such as adrenal insufficiency, infection/sepsis, alcohol abuse, organ failure, and insulinoma, may need to be considered. (One caveat is that fasting insulin levels may be higher in the presence of ESKD, and serum cortisol levels may be variable.) Although dextrose contained in the dialysate solution may work to offset falling glucose levels, acute hypoglycemia occurring during or immediately after the dialysis session may still require treatment with oral glucose or intravenous dextrose. If available, glucose 15–20 g should be administered; in more severe episodes, intravenous dextrose 50%, 10–50 mL. Reduction in insulin, especially after dialysis, or conversion to an oral agent with lower hypoglycemic risk, such as a thiazolidinedione or a dipeptidyl peptidase-4 inhibitor, may be necessary for consultation with the diabetologist. Glucagon kits for emergency use should be prescribed. Long-acting insulin may pose a prolonged risk. Nonselective beta-blockers may mask hypoglycemia symptoms and delay recovery from an episode.

Medications for Glycemic Control

Oral Hypoglycemic Agents

Providing ESKD management in patients with diabetes mellitus also requires awareness of medications used to achieve glycemic control. In recent years, an increasing number of hypoglycemic therapies have become available, with diverse mechanisms of action, primarily for patients with type 2 diabetes. In the general diabetes population, a patient-centered approach (i.e., prioritizing patient preferences, side effects, risk of hypoglycemia, cost) is currently recommended. However, the choice of oral therapies for managing diabetes is more restricted in the diabetic ESKD population (Table 49.3). There have been few substantive trials of oral hypoglycemic agents in ESKD. As a result, dosage uncertainties and contraindications make management of the ESKD patient difficult. One result is that medications may be underprescribed. A selection of recommended oral hypoglycemic agents in ESKD is reviewed in Table 49.3 (Multiple other classes and agents are omitted from the table because their use should be avoided in the ESKD patient. These include other sulfonylureas, biguanides, alpha-glucosidase inhibitors, other incretin-mimetics, and sodium/glucose cotransporter 2 [SGLT-2] inhibitors). It should be noted that SGLT-2 inhibitors, increasingly investigated and prescribed in recent years for type 2 diabetes, have no current indication in patients with end-stage renal disease and would not be expected to be effective.

TABLE 49.3 **Selection of Oral Antidiabetic Medications Recommended in ESKD**

Class	Compound	Drug Name	Formulations	Mechanism of Action	Primary Physiological Action	Advantages	Disadvantages	Renal Metabolism/ Elimination	ESKD Dose Range
Sulfonylureas	Glipizide	Glucotrol	5, 10 mg	Close K_{ATP} channels on β-cell membrane	• ↑ Insulin secretion	• Common Use	• Hypoglycemia • Weight gain • Low durability • ?Cardiovascular risk • Drug interactions	10% excreted unchanged in urine	2.5–10 mg daily
		Glucotrol XL	2.5, 5, 10 mg						
	Glimepiride	Amaryl	1, 2, 4 mg					Weakly active & inactive metabolites excreted in urine	1–4 mg daily
Meglitinides	Repaglinide	Prandin	0.5, 1, 2 mg	Close K_{ATP} channels on β-cell membrane	• ↑ Insulin secretion	• ↓ Postprandial glucose excursions • Dosing flexibility • Relative safety	• Hypoglycemia • Weight gain • Frequent dosing • High cost	Limited excretion of inactive metabolites	0.5–1.0 mg three times daily w/ meals
Thiazoli-dinediones	Pioglitazone	Actos	15, 30, 45 mg	Activate the nuclear transcription factor PPAR-γ	• ↑ Insulin sensitivity	• No hypoglycemia • Durability of effect • Favorable effect on lipid profile	• Weight gain • Possible fluid retention • ?Bladder cancer • Fractures • High cost	Limited excretion of active metabolites	15–30 mg daily

Continued

TABLE 49.3 **Selection of Oral Antidiabetic Medications Recommended in ESKD—cont'd**

Class	Compound	Drug Name	Formulations	Mechanism of Action	Primary Physiological Action	Advantages	Disadvantages	Renal Metabolism/ Elimination	ESKD Dose Range
DPP-4 inhibitors	Sitagliptin	Januvia	25, 50, 100 mg	Inhibit the inaction of endogenous incretins by DPP-4	• ↑ Insulin secretion • ↓ Glucagon secretion	• Well tolerated • No weight gain • Less hypoglycemia	• Effect is modest • ?Pancreatitis • Urticaria/ angioedema	Excreted mostly unchanged in urine	25 mg daily
	Saxagliptin	Onglyza	2.5, 5 mg					Renal excretion of drug and metabolites	2.5 mg daily
	Linagliptin	Tradjenta	5 mg					Very limited urinary excretion	5 mg daily
	Vildagliptin	Galvus	50 mg					Some excretion of drug by kidneys	50 mg daily
Incretin mimetics	Liraglutide	Victoza	18 mg/3 mL	Activates GLP-1 receptor	• ↑ Insulin secretion • ↓ Glucagon secretion • ↓ Gastric emptying • ↑ Satiety	• Weight loss • No hypoglycemia	• GI side effects • No experience in renal failure • Injection required • ?Medullary thyroid cancer • ?Pancreatitis • High cost • Weight loss	Endogenous enzymes throughout the body	0.6–1.8 mg SQ daily

DPP-4, Dipeptidyl peptidase-4; *ESKD*, end-stage kidney disease; *GI*, gastrointestinal; *GLP-1*, glucagon-like peptide 1; *PPAR-γ*, peroxisome proliferator-activated receptor γ; *SQ*, subcutaneous; ?, possible.

Insulin

Limitations of the oral hypoglycemic agents make insulin the most common therapy in the ESKD diabetic patient. In the general population, patients with markedly symptomatic hyperglycemia should already be on an insulin-based regimen. Furthermore, due to the progressive nature of type 2 diabetes, insulin therapy is eventually required in many. As CKD progresses in type 2 patients, the proportion solely relying on oral agents diminishes, and insulin use becomes greater. Principles of insulin therapy in patients with advanced CKD are not fundamentally different from those in patients without CKD, but it should be emphasized that insulin requirements may be lower and insulin action more prolonged. Endogenous insulin has a molecular weight of 6000 daltons and is significantly cleared by HD.

Compared to the general population, glycemic management with insulin becomes more complex in the ESKD patient. The general trend toward reduced insulin doses, as CKD progresses, is further complicated by issues such as improvements in insulin sensitivity with dialysis, clearance of insulin by the dialysis procedure, increased carbohydrate consumption as appetite improves, and exposure to dextrose in the HD solution (and, to a far greater extent in patients on PD, the high dextrose concentration in PD fluid). In a limited euglycemic clamp study, basal insulin requirements fell by 25% on the day after HD, with no change in bolus requirements. In recent years, dialysate dextrose concentrations have been reduced by half to 100mg/dL, possibly achieving less well the purpose of avoiding glucose loss during the treatment and helping to prevent hypoglycemia. CGM data have confirmed that glucose levels fall during the HD procedure. On the day of HD, morning insulin needs will be reduced, depending on food consumption. This effect may extend into the 24-hour period following the HD treatment.

New human insulin-derived analogs have been developed in recent years that reproduce the physiological basal and prandial insulin secretion in response to glucose (Table 49.4). Whether they can improve glycemic control while reducing hypoglycemia in ESKD remains to be determined. Long-acting insulin for basal coverage, combined with sliding scale nutritional coverage with short-acting insulin analogs ("basal-bolus"), is currently the standard of care in consensus guidelines for diabetes management. There are few pharmacokinetic data and an absence of therapeutic guidelines for insulin adjustments in advanced CKD. Rapid-acting analogs such as insulin lispro have a more rapid absorption and onset of action as well as shorter duration of action than regular human insulin. Long-acting insulin analogs such as glargine or detemir have delayed absorption. In ESKD patients who remain nephrotic, binding of insulin detemir to serum albumin after injection may make the clinical management more difficult. A regimen consisting of noninsulin oral agents and basal insulin is also commonly utilized in type 2 patients. Continuous insulin infusion via an insulin pump may improve glycemic control with less hypoglycemia risk, and an increasing number of type 1 diabetics and some type 2 diabetics on insulin are combining insulin pumps and glucose sensor technology. For all ESKD patients with diabetes, glycemic management primarily by an expert diabetologist is strongly recommended.

Hemodialysis Access

Current ESKD guidelines recommend early fistula placement followed by timely evaluation for maturation, and interventions as needed, as the optimal strategy for most patients, especially those under age 60 years. It is increasingly recognized that a fistula-first strategy is more effective when the likelihood of fistula maturation is higher. Patients with vascular disease, including those with diabetes as a comorbidity, are more likely to have higher rates of maturation failure. USRDS 2016 data indicate that access used for the

TABLE 49.4 Profiles of Available Insulins and Insulin Analogues

Insulin Type	Name	Example	Onset of Actions	Peak Effect	Duration
Basal	NPH	Humulin N	1–2 hours	4–8 hours	12–18 hours
		Novolin N			
	Glargine	Lantus	2 hours	No Peak	20–24 hours
	Detemir	Levemir	2 hours	3–9 hours	16–24 hours
Nutritional	Regular	Humulin R	30 minutes	2–4 hours	6–8 hours
		Novolin R			
	Lispro	Humalog	5–15 minutes	1–2 hours	4–6 hours
	Aspart	Novolog	5–15 minutes	1–2 hours	4–6 hours
	Glulisine	Apidra	5–15 minutes	1–2 hours	4–6 hours

Summary pharmacokinetic data are from individuals without moderate or severe chronic kidney disease.

first outpatient dialysis treatment was a fistula in 17% of those with diabetes as the primary cause, similar to other primary causes with the exception of cystic diseases, where fistula use was twice as common. For the 2017 prevalent population, diabetes was similar to other ESKD causes in fistula, graft, and catheter rates.

Nonetheless, diabetes is commonly identified as a negative predictor of both primary and secondary fistula patency, usability, and access flow rates and a positive predictor of access procedures and late fistula failure. Patients with diabetes have a lower mean cumulative access survival in some studies. In addition to cardiovascular factors such as increased arterial calcification and stenosis, mechanistic pathways may include prothrombotic factors, such as platelet aggregation, endothelial dysfunction, vascular intimal damage, oxidative stress, and altered matrix metabolism. Ischemia distal to the arteriovenous (AV) access is particularly common in patients with diabetes. Patients with diabetes are more likely to require dialysis initiation within 2 years of fistula placement; an extended time for maturation may improve fistula outcomes, but data are limited.

Nutrition/Protein Energy Wasting

Nutritional management in ESKD is addressed in Chapter. Dietary management of the CKD/ESKD patient becomes more complex in the patient with diabetes. Current guidelines regarding nutritional management in ESKD focus primarily on protein and energy balance and typically do not separately address the patient with diabetes. Low-carbohydrate diets, individualized ideal carbohydrate intake, carbohydrate counting, and consistent mealtimes are standard nutritional measures in diabetes. Multiple factors contribute to the nutritional and metabolic status of the diabetic patient with ESKD, including dietary deficiencies and protein-energy wasting. During CKD progression, diabetic patients may manifest generalized malnutrition and protein-energy wasting related to inadequate calorie/protein intake, gastroparesis, intercurrent illness, poor glycemic control, proteinuria, diarrhea, and other factors, compounded by endocrine abnormalities, such as insulopenia/insulin resistance. Uremic malnutrition, particularly decreases in serum biomarkers such as albumin and prealbumin, is more prevalent in diabetic ESKD patients and is associated with increased risk of hospitalization and death. Compared to nondiabetics, incident diabetic ESKD patients have higher lean body mass at baseline, followed by accelerated loss during the first dialysis year. What results is a higher risk of sarcopenia, including loss of muscle mass and reduced muscle strength, perhaps related to insulin deficiency. Contributors to metabolic protein depletion may include poor glycemic control, deficiency, or resistance to the anabolic actions of insulin, and subclinical inflammation. Preservation of muscle mass is the ultimate goal of management of this protein-energy wasting condition in CKD/ESKD patients. Dietary interventions may include high-protein meals or supplements or enteral feeding. Concerns about the glycemic burden of nutritional interventions may be relegated to a secondary status. During intercurrent illness, intensive nutritional support may be required. No large randomized clinical trials have evaluated the benefit of nutritional interventions, such as protein supplementation, appetite stimulants, and anti-inflammatory intervention, on outcomes in diabetic ESKD patients.

Hypertension

The prevalence of hypertension in individuals with diabetic kidney disease involves more than three-quarters of those with stage 5 CKD. Hypertension is frequently refractory, and per CKD guidelines, many will already be on renin-angiotensin-aldosterone system (RAAS) blockade. Nonetheless, there are no well-controlled studies of hypertension management in diabetic ESKD patients, which remains a public health priority. Consensus documents on hypertension in dialysis patients make minimal reference to the diabetic population. The optimal blood pressure target and regimen (including bedtime dosing of medications) in patients with ESKD due to diabetes are not adequately defined. Observational studies in the general ESKD population have suggested a U-shaped relationship between blood pressure and mortality. The association between low blood pressure in particular and mortality appears to be more pronounced in patients with diabetes. In patients with a recent myocardial infarction, beta-blockers are indicated, although the risk of hypoglycemia should be addressed.

Dialysis-Associated Hypotension

The most common patient-related factor reported in intradialytic hypotension is diabetes, likely attributable to a higher prevalence of cardiovascular complications and autonomic neuropathy. In patients with ESKD, intra- and postdialytic hypotension continues to play an important role in survival outcomes and likely affects quality of life, dialysis access failure, and cardiovascular events. The basis for the development of hypotension in this setting typically involves an abnormal reduction in blood volume, defective contraction of resistance vessels, and diminished cardiac output. Drops in both systolic and diastolic pressure during and after HD are both greater in HD patients, who have diabetes related to poor cardiac performance and small fiber peripheral neuropathy. The normal compensatory response to erect posture is a modest fall in systolic pressure and an increase in diastolic pressure and pulse rate. Orthostatic hypotension, which occurs following intermittent HD, may be defined as a fall in systolic blood pressure by 20mm Hg or more with upright posture. The most common symptoms are cramps, nausea/vomiting, and dizziness. Complications include stroke and angina. Evaluation of the diabetic dialysis patient with hypotension should include

a review of volume status, target weight, hemoglobin/hematocrit, and cardiac status. Multiple medications may contribute, including alpha-adrenergic blockers, vasodilators, anti-anginals, antidepressants, narcotics, sedative/hypnotics, antipsychotics, and phosphodiesterase inhibitors. Management of dialysis-associated hypotension in the diabetic patient has evolved, as hypertonic saline has become less available in the dialysis facility, and higher dialysate sodium concentrations (> 140 meq/L) have fallen into disfavor. Initial steps are to reduce or cease ultrafiltration and infuse isotonic saline. Sitting and standing blood pressures should be closely monitored, and the transition postdialysis from a supine to standing position observed. Potential offending agents must be evaluated. Custom-fitted elastic stockings should be obtained. Fludrocortisone acetate is a synthetic mineralocorticoid that may improve hypotension in ESKD by amplifying catecholamine effects to increase peripheral vascular resistance. Midodrine, a direct alpha-1 adrenoreceptor agonist, is the only peripheral selective agent approved by the Food and Drug Administration (FDA) for orthostatic hypotension. Midodrine is a prodrug but is rapidly absorbed, and its peak action is 1 hour after ingestion. The dose range is 2.5 mg to 10 mg tid. The potential side effects of midodrine include angina, pilomotor reactions, pruritis, supine hypertension, GI complaints, and urinary retention. Droxidopa is a prodrug to the neurotransmitter norepinephrine that is now indicated for HD-induced hypotension. Clinical trials suggest that its effectiveness is similar to midodrine while causing less supine hypertension.

Cardiovascular Disease

According to the American Heart Association (AHA), diabetes mellitus is designated as a major risk factor for cardiovascular disease because all patients with diabetes have a risk of coronary heart disease equivalent to those who have already had a coronary occlusive event. Diabetes is considered an independent risk factor for several forms of cardiovascular disease, including atherosclerotic coronary heart disease, cardiomyopathy, and stroke, and the risk of major adverse cardiovascular events (MACEs) is higher. The heightened cardiovascular risk is exaggerated as the severity of kidney complications becomes greater. Cardiovascular death risk decreases with increasing age, with hazard ratios (HRs) ranging from 2.5 (over 75 years of age) to a markedly elevated HR of 30 (under 55 years of age). Remarkably, cardiovascular disease is listed as a cause of death in roughly two-thirds of individuals with diabetes.

Cardiovascular disease is also a leading cause of death in diabetic ESKD patients, even in young adulthood. Individuals with both diabetes and ESKD are more likely to have a cardiovascular event (myocardial infarction, heart failure, stroke) than those with either condition alone. When compared to the general population, they are at greater risk of sudden cardiac death. Diabetic ESKD patients are more likely to die after an acute myocardial infarction than are nondiabetics. For clinicians, assessment of cardiovascular risk through identification of potentially remediable risk factors should be the first step in reducing clinical risk in diabetic ESKD patients. According to the AHA, risk assessment must consider major risk factors (hyperglycemia, hypertension, abnormal serum lipids, smoking) as well as predisposing conditions (family history, physical inactivity, excessive body weight, abnormal obesity pattern). In addition, limited data have suggested that increased risk may be associated with certain oral hypoglycemic agents, as opposed to insulin.

Practice guidelines increasingly classify ESKD as a coronary risk equivalents. For diabetic ESKD, coronary prevention is, therefore, secondary prevention. However, current treatment guidelines pertaining to ESKD do not support initiation of statin therapy in dialysis patients, although they may be continued when dialysis is initiated in those already under treatment. Kidney Disease, Improving Global Outcomes (KDIGO) and other guidelines, indicate that statins for secondary prevention in diabetic ESKD are not effective; although post hoc analyses of AURORA and 4-D trials restricted to the occurrence of cardiac events have suggested benefit with statin therapy. There is no evidence of excessive side effects of statins in diabetic ESKD.

Infection

Clinical evidence points to impaired host defenses and a higher prevalence of infection in both diabetes and ESKD. USRDS data indicate that septicemia and other infections account for about 10% of attributable mortality rates. Mortality rates due to sepsis are almost twice as high in diabetes. Mortality caused by sepsis is approximately 50 times greater with diabetic ESKD compared to diabetes in the general population. Diabetic ESKD patients should therefore be considered a high-risk group for the development of infection, including lethal sepsis. Susceptibility in diabetes is related to impaired host defenses such as immune dysfunction caused by the hyperglycemic environment, vascular disease, GI dysmotility, and poor antibacterial activity in urine. Immune defects include impeded production of interferon, diminished antimicrobial effects of macrophages, impaired complement activation, and reduced production of interleukins. Examples of infections associated with diabetes include the urinary tract (emphysematous cystitis, pyelonephritis, perinephric abscess, fungal infection), lungs (pneumonia, influenza, tuberculosis), GI system (emphysematous cholecystitis, esophageal candidiasis), and soft tissues (foot infections, necrotizing fasciitis, surgical wound infections). Because infection can worsen glycemic control, further enhancing susceptibility to infection, glycemic control should be achieved. Anti-influenza and -pneumococcal vaccination are strongly recommended, along with routine screening for tuberculosis, regular foot examinations, proper wound care, and aggressive evaluation/management of febrile episodes.

Peripheral Arterial Disease/Foot Ulcers

Peripheral artery disease (PAD) is more common than myocardial infarction in CKD patients but is underdiagnosed, in part because of a lack of lower extremity symptoms. Three independent risk factors place the patient with diabetes and ESKD at risk for lower limb complications: peripheral arterial disease, neuropathy, and increased susceptibility to infection. In addition, uremic myopathy may result in wasting of the intrinsic foot muscles and development of high plantar pressures. Commonly used criteria to identify PAD in the diabetic ESKD patient include assessment of peripheral pulses, Doppler waveforms indicating poor monophasic waveform or the absence of flow, and toe blood pressures. The ankle/brachial index (ABI) is determined by dividing the blood pressure in the ankle by that in the brachial artery. An ABI of ≤ 0.90 indicates PAD, while a falsely elevated value of over 1.30 suggests a calcified, noncompressible vessel, weakening the sensitivity of ABI in detecting PAD. Thus, when both occlusion and stiffness are present, the diagnostic sensitivity of the Ankle Brachial Pressure Index (ABPI) is reduced. In diabetic ESKD, low ABI loses its predictive value because of the high prevalence of arterial stiffness. As a consequence, reliance on physical exams is even more important.

The diabetic foot is one of the most frequent and feared complications of diabetes, with an estimated lifetime risk estimated at 25%. Foot complications are twice as common in those with ESKD. Loss of protective sensation makes the patient vulnerable to unrecognized foot tissue injury. In the general diabetic population, routine foot screening combines risk stratification and intervention to prevent complications. The American Diabetes Association recommends annual foot monitoring and care. Unfortunately, dialysis patients are less likely to inspect their feet or attend podiatry clinics. Multidisciplinary diabetic foot care should be integrated into the comprehensive dialysis care of the diabetic ESKD patient. An evaluation that can be incorporated into the dialysis setting should include the status of distal sensation and history of lower-limb interventions, early signs of infection and ulcer formation, vascular insufficiency, and light-touch examination of the toes.

The rate of amputations is 6–10 times higher among diabetic patients with ESKD. Diabetic dialysis patients are more likely to require major amputations (below-knee and above-knee) and suffer death following amputation surgery. Lower extremity amputations are preventable through patient education, proper foot hygiene, therapeutic footwear, and regular foot surveillance consisting of full assessment at dialysis initiation, followed by monthly foot evaluations for warning signs. The most important factors to be evaluated when confronted with foot ulcers are the presence of peripheral arterial disease, peripheral neuropathy, and foot deformities.

Risk factors for major amputations are extensive infection, heel ulcers, poor vascular run-off, and low ejection fraction. Open wounds or ulcers worsen neuropathic pain, and vascular compromise is an indication for urgent referral to a foot specialist or vascular surgeon. Lower extremity revascularization in diabetic ESKD patients may be complicated by infection, impaired wound healing, increased perioperative mortality rates, and reduced lower extremity salvage and patient survival. Even after successful postamputation rehabilitation, mortality risk is increased. Endovascular revascularization may be appealing as first-line therapy over open bypass surgery for achieving improved blood flow to the ulcer area. Prevention programs should especially be emphasized for individuals at the highest risk (diabetic ESKD with previous ulceration or amputation).

Neuropathy

The most common cause of neuropathy in ESKD is diabetes. Recent guidelines acknowledge that diabetic and uremic neuropathies may have similarities. In addition, insofar as effective treatments are lacking, screening and prevention take on added significance. Important neurological complications in diabetic ESKD include cardiovascular autonomic neuropathy (CAN) and diabetic peripheral neuropathy. Most common in diabetes is distal symmetric polyneuropathy (DSPN), the presence of distal sensorimotor nerve dysfunction. DSPN in the form of sensory loss or neuropathic pain may occur in up to half of patients with diabetic ESKD. DSPN may also be complicated by neuroarthropathy (Charcot foot) and is a major contributor to foot ulceration and falls/fractures. First-line pharmacologic treatment for neuropathic pain is a calcium channel alpha-2-delta ligand, such as pregabalin or gabapentin. Pregabalin has regulatory FDA approval for treatment of neuropathic pain in diabetes. Compared to gabapentin, pregabalin has a more rapid onset of action and limited dosing range; a dosage reduction and supplemental postdialysis dose are appropriate in ESKD. However, it is not available in generic form, and cost may be prohibitive. Gabapentin is commonly used off-label, but because of renal excretion, the dose must be titrated carefully and limited to a maximum of 1800 mg/day. Signs of toxicity include myoclonus and central nervous system (CNS) effects such as dizziness, ataxia, and altered consciousness. At recommended doses, the risk of dependence and addiction to pregabalin and gabapentin are low. The selective serotonin-norepinephrine reuptake inhibitor duloxetine is also approved for painful DSPN but should be avoided in ESKD. Opioids are effective but with long-term use cause limiting side effects, such as constipation and impaired cognitive function, and tolerance/addiction may occur. Hydromorphone, fentanyl, and methadone are safest in ESKD, and the latter is more effective due to its antagonism of the *N*-methyl-D-aspartate (NMDA) receptor. Compared to other opioids, tramadol has a lower potential for abuse. Tramadol is relatively well tolerated in doses up to 200 mg/day, with no postdialysis supplemental dose.

Major clinical manifestations of diabetic autonomic neuropathy are cardiac and GI. Cardiac autonomic neuropathy (CAN) can have important clinical implications and may

present with resting tachycardia, fixed heart rate, exercise intolerance, intradialytic hypotension, orthostatic hypotension, or silent myocardial ischemia. Sympathetic overactivity is characteristic of CAN. Conclusive evidence supports CAN as an independent predictor of mortality. CAN treatment is based on prevention with glycemic control and on alleviating symptoms depending on the clinical manifestation. The only current method likely to improve CAN is strict glycemic control, particularly in type 1 diabetes. Some studies suggest the beneficial effects of HD on heart rate is variability due to CAN. Beta-blockers may provide protection from cardiovascular events. Treatment of orthostatic hypotension in ESKD is challenging, especially when the patient has coexisting hypertension that is being treated (see earlier).

Another major clinical manifestation of diabetic autonomic neuropathy is gastroparesis. One of the major causes of protein malnutrition in diabetic ESKD, dysmotility, may affect all segments of the GI tract. Diabetic gastropathy includes gastroparesis or delayed emptying of ingested nutrients in the absence of gastric outlet obstruction and other dyspeptic conditions found in patients with diabetes. Overall, about half of type 1 and a third of type 2 patients have gastroparesis. Gastroparesis itself causes nonspecific symptoms of nausea, vomiting, anorexia, early satiety, and postprandial abdominal discomfort. In the general diabetic population, gastroparesis is associated with protein malnutrition and more frequent hospitalizations. It places patients at risk for weight loss, impaired drug absorption, poor quality of life, and probably increased mortality rates. It may be further exacerbated by HD and PD. Episodes may be triggered by poor glycemic control (which delays gastric emptying), medication intolerance, infections, and noncompliance with medications. Delayed gastric emptying on scintigraphy of digestible solids over 4 hours after food intake is the hallmark diagnostic finding. Complications include electrolyte disturbances and volume depletion; upper endoscopy may be indicated to rule out coexisting esophagitis, Mallory-Weiss tears, and bezoar formation. Fluctuations in gastric emptying will affect periprandial glucose concentrations and make glycemic control more difficult. Prompt hospitalization is required in cases of dehydration and DKA.

After stabilization, the treatment approach includes modification of diet, correction of hyperglycemia, and use of prokinetic agents. Dietary therapy includes low-volume, frequent soft or liquid meals with low fat and fiber content. Drugs that affect GI motility, such as opioids, should be withdrawn. Metoclopramide, the only prokinetic approved for the treatment of gastroparesis, is a dopamine antagonist with central antiemetic and peripheral gastric prokinetic actions. It improves the acute effects of gastroparesis in about half of patients but with a high incidence of dose-dependent extrapyramidal effects, such as dystonic reactions and tardive dyskinesias. The initial dose is 5mg preprandial. A related dopamine antagonist, domperidone, is not approved in the United States. Oral or intravenous erythromycin, used as a promotility agent, accelerates gastric emptying and improves bloating, although the oral formulation may result in its own GI side effects. Ondansetron orally may improve intractable symptoms. Options in resistant cases include botulinum toxin injection, gastric stimulation, surgery, or vagotomy.

Ophthalmologic Complications

Diabetic retinopathy is a specific microvascular complication of both type 1 and type 2 diabetes. The prevalence of diabetic retinopathy among ESKD patients is high. For decades, proliferative diabetic retinopathy has been successfully treated with panretinal laser photocoagulation. The majority of diabetic CKD patients have had laser photocoagulation therapy before reaching ESKD. Background retinopathy may cause visual impairment leading to blindness when the macular area is involved. Even more damaging is proliferative diabetic retinopathy, with neovascularization as well as vitreous hemorrhage.

Patients attending specialist diabetes clinics are more likely to be screened for retinopathy. Comprehensive eye examination with high-quality fundus photography by an ophthalmologist is indicated within 5 years of onset of type 1 diabetes and soon after the diagnosis of type 2 diabetes. Frequent eye examinations are recommended but continue to be uncommon among ESKD patients with diabetes, with low rates of diabetic eye examinations after dialysis initiation; only one in five receive two tests per year. In those without retinopathic findings, follow-up should be every 2 years, and in those with retinopathic findings, at least annually. Hypertension accelerates the progression of diabetic retinopathy, adding to the urgency of treatment of high blood pressure readings in diabetic ESKD patients. Diabetic retinopathy is not a contraindication to aspirin therapy. Heparin in doses required for dialysis anticoagulation does not appear to be associated with acceleration of diabetic retinopathy. Recent advances in retinal imaging and new treatments may further improve the ocular care for patients with diabetic ESKD. Noninvasive assessment of retinal structures has improved the identification of patients at risk for vision loss. Recent studies have demonstrated the potential benefit of anti-vascular endothelial growth factor (VEGF) treatment.

Home Hemodialysis

For over a decade, there has been increased interest in home HD (HHD), with the total number of HHD patients rising, although they continue to represent a relatively small portion of HD patients and even of home patients. Furthermore, available data from USRDS and meta-analyses of published studies indicate that patients with diabetes as the primary renal diagnosis are somewhat underrepresented in the ESKD population on HD. The USRDS data indicate that one-third of patients on HHD had diabetes as a primary diagnosis. In the Canadian Multicenter Nocturnal

Home Hemodialysis Cohort (1994 to 2006), the entire cohort tended to be younger and less likely to have diabetes than the general ESKD population. Only 12% had diabetes. Potential benefits in diabetic ESKD patients include reduced strain on the heart and avoidance of intradialytic hypotension. Comparative outcomes data with nondiabetic ESKD patients are lacking. In the Canadian study cited earlier, however, diabetes was a powerful predictor of death or treatment failure and was equivalent to the addition of 14.5 years of age.

Peritoneal Dialysis

PD is a viable alternative to HD for patients with diabetic ESKD. USRDS data for the year 2016 report that about 7% of prevalent dialysis patients due to diabetes are on the peritoneal modality, versus about 8% for glomerulonephritis and about 7% on dialysis with all diagnoses. As in patients without diabetes, selection of a dialysis modality in patients with diabetes is known to depend on factors such as comorbidities, creation of dialysis access, hemodynamic stability, tolerance of the dialysis modality, and functional level. In addition, cognitive impairment common in diabetes may interfere with self-performance of PD. The presence of diabetes modifies both the potential advantages and disadvantages of PD in ESKD patients. The benefits of PD, including slower, more sustained ultrafiltration, lack of need for vascular access, and slowing of residual renal function decline, are particularly applicable to patients with diabetes. The reduction in circulatory stress with its perfusion abnormalities affecting organ systems such as the heart, brain, kidney, and retina may have special advantage. Extra disadvantages include the enhanced metabolic effects of obligatory glucose absorption, including hyperglycemia, hyperlipidemia, obesity, and systemic insulin resistance; increased accumulation of advanced glycation end-products, particularly in the peritoneum itself; and worsening of GI side effects including esophageal reflux and gastroparesis. Recent analyses suggest that PD patients, in general, may have a higher risk of myocardial infarction compared with HD patients. In addition, patients with diabetes may have ongoing extracellular volume excess on PD.

Glucose absorption during PD commonly exceeds 100 g per exchange. A correlation between the concentration of dialysate dextrose and daily mean glucose concentrations by CGM has been demonstrated. Higher prescribed peritoneal dialysate glucose may be associated with overall risk of death and the need to transfer to HD. Poor glycemic control appears to be associated with incrementally higher mortality in PD patients with diabetes. Glucose-sparing regimens have been developed in order to reduce the peritoneal and systemic exposure to glucose. Icodextrin, for example, achieves greater ultrafiltration with less glucose exposure. A recent multinational, randomized controlled study supported the use of glucose-sparing solutions (icodextrin, amino acid-based dialysate) compared to dextrose in diabetic patients. Icodextrin has been shown to improve metabolic and fluid management in high-transport diabetic patients. An important caveat is that patients treated with icodextrin are at risk for having overestimation of blood glucose measurements when testing with glucose dehydrogenase/pyrroloquinolinequinone cofactor (GDH/PQQ) glucometers, likely due to assay interference by circulating maltose metabolites of the icodextrin.

Basal-bolus insulin regimens are most commonly used for glycemic management. Intraperitoneal insulin use is not popular with most nephrologists, although meta-analysis data indicate that it can improve glycemic control. However, for diabetic patients requiring PD, the option of adding insulin to peritoneal dialysate solutions prior to infusion provides coverage of dialysate dextrose exposure, allowing some patients to avoid insulin-dependent injections and reducing insulin requirements in others. Intraperitoneal insulin is absorbed into the portal system and results in more physiologic delivery than with intermittent subcutaneous injections, better inhibiting hepatic gluconeogenesis and ketogenesis. However, full conversion of subcutaneously treated patients to intraperitoneal insulin will require up to fourfold more insulin, as absorption to the tubing set and catheter is significant. Other possible disadvantages of intraperitoneal insulin include increased risk of bacterial contamination/peritonitis, lowered plasma high-density lipoprotein (HDL) levels, rare complications of peritoneal fibroblast proliferation, hepatic steatosis, malignant omemtum syndrome, and increased cost. Use of intraperitoneal insulin appears to have further diminished with the advent of continuous cycling peritoneal dialysis (CCPD), out of concern for greater risk of nocturnal hypoglycemia and the lack of information on higher insulin dosing required for substantially larger bag volumes. When intraperitoneal insulin is instituted to cover dextrose exposure during overnight exchanges, regular human insulin is the standard, in incremental doses of 2 to 12 units per liter. Rapid-acting insulin analogs should be avoided.

Kidney Transplantation

Patients with ESKD due to diabetes, particularly type 2, have a lower probability of receiving a kidney transplant. Although replacement or preemption of dialysis by kidney transplantation presents the best hope for improved survival and quality of life in diabetic ESKD patients, access to transplantation for these patients remains significantly reduced. ESKD patients with diabetes are less likely to be referred for transplantation, suggesting that the presence of diabetes continues to limit access to transplant waiting lists. For year 2016, about 17% of prevalent diabetic ESKD patients had transplants and were off dialysis, compared to almost 30% for the total ESKD population. Transplant rates into recipients with diabetes, for both living and with deceased donors, remain low; while absolute numbers of kidney transplants into recipients with diabetes remains high

due to the preponderance of ESKD attributed to diabetes, compared to about half of patients with ESKD in general, and about one-fifth with diabetic ESKD have a functioning transplant.

Patient and graft outcomes of patients with diabetes treated with kidney transplantation remain inferior to those without diabetes, primarily related to higher cardiovascular and infection-related deaths, even in the first year following transplantation. Immunosuppressed diabetic recipients are more susceptible to infections than other populations. Infections may include highly lethal fungal causes such as mucormycosis. Peripheral vascular disease and increased risk of fractures contribute further to the burden of care. However, a recent retrospective analysis from a single large center suggested that significant reductions in cardiac events and infectious deaths in diabetic recipients were evident in recent years, unrelated to selection of lower risk candidates, while similar improvements were not noted in recipients without diabetic ESKD. Nonetheless, 5-year mortality rates in recipients with type 2 diabetes are twice those for nondiabetics. Consistent with findings in nondiabetic recipients, preemptive transplantation with diabetes rather than dialysis followed by transplantation is associated with improved survival. Also consistent with other ESKD groups, there is also an association between risk of graft loss and increasing time on dialysis in patients with diabetes. When type 1 diabetic patients are studied separately, mortality rates after initiation of dialysis increase exponentially after starting dialysis, and preemptive transplantation results in superior outcomes. For patients with type 1 diabetes who may qualify for a kidney transplant, it has therefore been recommended that the patient should be referred for kidney transplantation when their eGFR reaches 25 mL/min/1.73 m^2. Posttransplant, diabetic nephropathy may recur, although risk factors remain unclear. It should be noted that under conventional immunosuppressive regimens, up to 20% of recipients will develop posttransplant diabetes.

Comprehensive Conservative Care

Data indicate that about three-quarters of all patients with ESKD are treated with dialysis. The likelihood of initiating dialysis actually appears to be increased in patients with diabetic CKD. However, because the survival advantage of dialysis care may be limited, particularly for older individuals with diabetes, comprehensive conservative care remains an alternative. The survival advantage associated with dialysis is reduced in older individuals with comorbidities such as diabetes. However, evidence on overall outcomes as compared to conservative care remains limited.

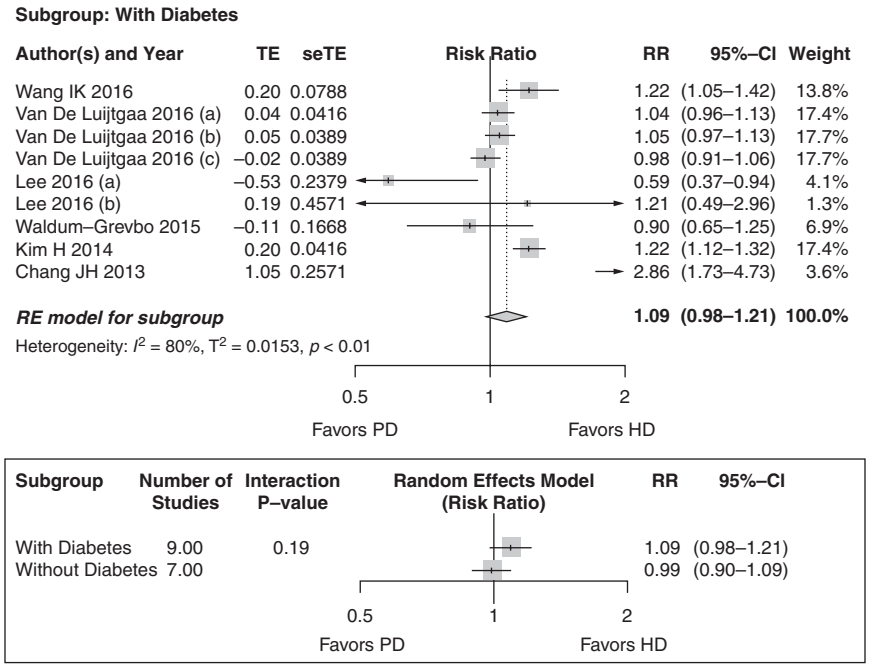
Outcomes

Among all HD patients, the overall hospitalization rate is one per approximately seven patient/months. Patients who have diabetes as their primary cause of ESKD have a higher risk of all-cause hospitalization, about once every 6 months, and a similar degree of risk increase for cardiovascular and infection (but not vascular access infection) causes. Overall mortality rates for ESKD patients have continued to decline over the past two decades. However, USRDS data on patients 65 years or older indicate that improvements in survival the past 20 years have been significantly less in patients with diabetes. Diabetes continues to carry the highest mortality rates of all primary CKD diagnoses requiring renal replacement therapy. Adjusted survival probabilities after initiation of ESKD treatment begin to be worse for diabetes as primary ESKD cause around 24 months. By 60 months, survival probability is 37%, 6.4 percentage points lower than for hypertension and 16.6% lower than for glomerulonephritis. The mortality rate with type 1 diabetes increases exponentially following transition to dialysis. Patients with diabetic ESKD have the greatest number of comorbid conditions. Cardiovascular disease (acute myocardial infarction, heart failure, stroke, malignant arrhythmias, sudden death), the leading cause of death in the general ESKD population, is twice as common in ESKD patients with diabetes. Increased risk of mortality occurs similarly in patients with diabetes mellitus as primary renal disease and diabetes as a comorbid condition, compared to the prevalent ESKD population. Recent data suggest that poor glycemic control during the pre-ESKD period is associated with higher 1-year ESKD mortality. Withdrawal from dialysis as a cause of death is more common with diabetics.

Studies comparing patient survival between HD and PD for diabetic patients have yielded conflicting results. A frequently cited observational ESKD study (45% with diabetes) indicated a higher mortality risk with HD among younger diabetics with no comorbidities and lower mortality risk with HD in older diabetics, whether comorbidities were present at baseline or not. A study utilizing more advanced statistical methods also showed a survival disadvantage for diabetics with at least one comorbidity or older than 65. A large recent systematic review of 17 cohort studies spanning the years 1993–2014 based on a propensity-matching strategy indicated that PD and in-center HD carried similar survival rates (Fig. 49.3). Another systematic review using databases found no mortality advantage in diabetes between PD and HD but suggested that PD as first choice might convey a higher death risk in elderly and frail patients.

Quality of Life

The impact of combined long-term illnesses of diabetes and CKD on health-related quality of life (HRQOL) has been addressed in several reports. While it is an important issue, few studies have compared health-related quality of life in ESKD patients with and without diabetes. Available data do indicate that patients with ESKD secondary to diabetes have worse



• **Fig. 49.3** Forest plot for meta-analyses of PD versus HD propensity-matched mortality comparisons. *CI*, Confidence interval; *HD*, hemodialysis; *PD*, peritoneal dialysis; *RE*,; *RR*, risk ratio; *sTE*, standard error of treatment effect; *TE*, treatment effect. (From Elsayed ME, Morris AD, Li X, et al. Propensity score matched mortality comparisons of peritoneal and in-centre haemodialysis: systematic review and meta-analysis. *Nephrol Dial Transplant.* 2020;1:1–11.)

health-related quality of life, inferior functional status, and lower physical aspects of HRQOL. One recent study indicated that both physical and mental components were inferior in HD patients with diabetes. Interventions to improve HRQOL (other than kidney transplantation) require further exploration.

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Care of Elderly Dialysis and End-Stage Kidney Disease Patients

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Introduction

Individuals aged 65 years or older comprise a significant proportion of those presenting with kidney failure and starting dialysis. In this chapter, we summarize data relating to key geriatric syndromes that are more commonly seen with kidney failure and discuss how these data can be integrated into advance care planning (ACP) discussions.

Functional Changes, Social Functioning, and Quality of Life

Large prevalence studies estimate that around 60% of hemodialysis (HD) patients 80 years of age or more require assistance with personal activities of daily living. Similar data are available for patients maintained on peritoneal dialysis (PD). Particularly in those who have baseline functional limitations or requiring nursing home placement prior to dialysis initiation, a more rapid decline occurs within the first few months after dialysis initiation. Dialysis-related factors that likely contribute to this rapid functional loss include postdialysis fatigue, the burden of the treatments themselves, the number of hours spent immobile in a dialysis chair, and bone and muscle changes that accompany metabolic bone disease. Regardless of the cause, this functional impairment is associated with lower quality of life as measured on the physical component summary score of the 36-Item Short Form Survey (SF-36), higher frequency and duration of hospitalizations, and a markedly lower survival. Thus, functional status and social functioning assessment are important components of prognostication.

Exercise Training and Geriatric Rehabilitation

All patients, regardless of age group, should be reminded of the benefits they may gain from exercise training. Simple home-based programs, such as that used in the EXerCise Introduction To Enhance Performance in Dialysis (EXCITE) trial, can stimulate sufficient activity and mobility to be beneficial to both physical and mental health, particularly if maintained over longer periods of time. Exercise training while on dialysis can be provided by physiotherapists and occupational therapists if resources exist. Alternatively, it can be done independently, at home, or in the dialysis center, with readily available equipment such as leg resistance bands, light weights, or seated stationary bikes. Intradialytic exercise training programs have been shown to improve physical performance measures such as the 6-minute walk and timed up-and-go tests. Common cited barriers to participating in such programs include dialysis-related fatigue, lack of motivation, concern over intradialytic exercise safety, impact on dialysis staff workload, and reluctance to routine changes.

Geriatric rehabilitation is a well-defined area with good evidence for its efficacy. Interdisciplinary rehabilitation teams with expertise in caring for geriatric patients are usually involved. Rehabilitation can be provided in the inpatient or outpatient setting; however, inpatient geriatric rehabilitation programs may particularly help reduce the functional decline that occurs in association with dialysis initiation. Recent studies have shown that inpatient rehabilitation was associated with fewer patients requiring prolonged care in a skilled nursing facility or long-term care home. More than two-thirds experienced a clinically meaningful improvement in function with inpatient rehabilitation (defined as meeting all predetermined functional goals), while 90% met at least half the goals they had set by the time of discharge. Ideally, dialysis times should not conflict with times when the patient is most active and willing to participate in rehabilitation therapy. Rehabilitation has also been shown to be more effective if dialysis is provided on a strict schedule, with some suggestions that the use of short daily dialysis (i.e., 2 hours, 6 days a week) may be more effective.

Cognitive Impairment and Dementia

Cognitive impairment refers to a change in brain function that affects, among other things, memory, attention, and the ability to process and execute mental tasks. Dementia is the progression of cognitive impairment such that it impairs the ability to complete daily functional tasks. Patients with cognitive changes who are still able to maintain independence despite cognitive changes, regardless of how severe, are considered to have the clinical syndrome of Mild Cognitive Impairment.

Cognitive changes are common among dialysis patients, appearing both at an earlier age and progressing more rapidly than what is typically seen in the general population. Prevalence studies have documented that almost 75% of patients maintained on dialysis have moderate to severe impairment when screened using standard psychometric test batteries. Similar prevalence rates are seen across both HD and PD patient populations, as well as those undergoing frequent short daily or nocturnal HD. In addition, studies suggest that the progression of cognitive impairment is accelerated in the presence of kidney disease, with emerging evidence that dialysis treatments themselves may contribute to this accelerated progression. Multiple studies, using Doppler, magnetic resonance imaging (MRI), and positron emission tomography scans, have shown that within an hour of starting HD, patients experience changes in cerebral hemodynamics and decreased brain tissue oxygenation. Cerebral blood flow drops by up to 15% from baseline during dialysis, contributing to chronic, frequent, and recurrent episodes of cerebral ischemia or "stunning." MRI findings in individuals undergoing maintenance HD, even if asymptomatic, include multiple lacunar infarcts and cerebral atrophy.

Clinical Impact of Cognitive Changes

Several studies have shown that mortality, morbidity, and need for long-term care are higher in those with chronic kidney disease (CKD) and cognitive impairment. At the individual patient level, cognitive decline alters how well patients can manage self-care activities. Cognitive changes can indirectly impact health and quality of life. Executive dysfunction, as opposed to, for example, memory impairment, is one of the cognitive domains more commonly affected in dialysis patients, and consequently, tasks requiring planning, organization, self-control, and adaptability to change are differentially impacted. Health-related tasks, including medication and diet management, dialysis modality selection, and advance care planning (ACP), are also affected. Even mild cognitive changes are associated with a lower likelihood of being accepted to the kidney transplant waitlist and, in those who do get waitlisted, with lower survival to transplant surgery. Consequently, it is important to assess cognitive function prior to discussions about ACP, modality selection, survival prognosis, and future wellbeing.

Cognitive Assessment and Screening

Typical assessments done during routine dialysis sessions identify only a fraction (< 5%) of patients with cognitive impairment. As a result, it is recommended that some form of cognitive screening be included, although frequency and methods are left to the individual clinicians. There are several screening tests available that have been used in the clinical dialysis unit setting, including the Mini-Mental State Examination (MMSE), 3MS, Rowland Universal Dementia Assessment Scale (RUDAS), Montreal Cognitive Assessment (MoCA), and Mini-COG. The MMSE is less useful in highly educated patients, those with language or cultural barriers, or those with predominantly executive dysfunction. The 3MS is a modified version of the MMSE with four additional items that improve discriminatory power, particularly those with a higher level of education. The Mini-COG is a simple bedside test that is practical and favored because of its ease of use and short administration time. Finally, the RUDAS is the optimal tool for patients with educational, language, or cultural barriers. Based on recent data, the MoCA may be the most optimal single screening tool for use in the dialysis unit setting. It appears to be more generalizable, sensitive, and specific when compared with other tools. Ideally, the MoCA should be performed, in a quiet secluded area, either on a nondialysis day or within the first hour of dialysis (to minimize the possible impact of cerebral stunning on the test's interpretation). Testing must be performed by trained individuals. A number of translated versions are available for those with language or cultural barriers, and a $MoCA_{BLIND}$ version can be used for those with visual limitations. The recommended frequency and duration of screening remain unclear.

Management of Mild Cognitive Impairment and Dementia

Both nonpharmacologic and pharmacologic treatments have been used in the general population, with modest effects. Nonpharmacological interventions include cognitive rehabilitation and exercise programs. While useful, these can be challenging to organize around dialysis schedules. Collaboration with a geriatric specialist or occupational therapist to educate and support caregivers, assist with managing pharmacologic options, and help access community programs to maximize function and safety is advised. Pharmacological therapies, such as cholinesterase inhibitors prescribed to patients with mild-to-moderate dementia and the *N*-methyl-D-aspartate (NMDA) inhibitor memantine given to those with moderate to severe dementia, show, at best, modest effects at slowing the rate of deterioration (especially in the setting of probable Alzheimer disease). Side effects are dose dependent and include gastrointestinal, neurologic, and cardiovascular side effects related to cholinergic stimulation (the most common being dizziness and drowsiness). Also concerning are theoretical risks of weight loss, debility, and syncope. Unfortunately, only a

few case reports using pharmacological interventions in dialysis patients have been published, so, if prescribed, patients should be monitored both for clinical benefit and for side effects. One additional concern of prescribing additional medications is increasing polypharmacy, noting that dialysis patients already have a heavy drug burden (see Polypharmacy section).

Behavioral and Psychological Symptoms of Dementia

Dementia is a progressive disease that may result in complex and often severe behavioral abnormalities. Sometimes referred to as behavioral and psychological symptoms of dementia, they encompass perceptual, emotional, or behavioral alterations such as hallucinations, repetitive movements, apathy, or impulsive behaviors (among others). Sometimes, patients can present with aggressive or unexpected actions, such as screaming or hitting, which can be dangerous for staff, the patient, and other patients, particularly within an HD center. Clear unit policies around the provision of dialysis and safety plans are advisable when patients begin to manifest these symptoms. It is advantageous to have previously had discussions with the family about the risk of behavioral and psychological symptoms of dementia.

A diagnosis of cognitive impairment or dementia presents an opportunity for the dialysis team to engage formally in ACP with patients and their families (see Advance Care Planning section). Families should be provided with ongoing education and counseling around the natural history of dementia and encouraged to identify opportunities and barriers that impact patient safety and quality of life. Frequent meetings to discuss changes and future circumstances under which dialysis discontinuation would be appropriate are necessary. It is important to ensure that families understand dementia as a terminal illness with a limited lifespan. Median life expectancy for nondialysis patients with dementia is approximately half that of age-matched patients; with both dialysis and dementia, this is substantially lower.

Depression

In both the elderly nondialysis and dialysis populations, depression is associated with functional decline, higher morbidity, greater risk of developing dementia, and lower survival. Prevalence rates are likely underestimated, as depression can mimic or result from dementia, making the diagnosis more challenging. Observational data suggest that patients with depression and CKD are at a threefold increased risk of progression of kidney disease to dialysis initiation, while for those established on dialysis, depressive symptoms are associated with higher mortality risk. Dialysis discontinuation and rates of suicide completion are approximately 1.5-fold higher in older dialysis patients than age-matched individuals from the general population.

Clinical Presentation of Depression

In dialysis populations, up to 30% of cases of depression appear to go unrecognized or untreated. Elderly patients with depression may present predominantly with fatigue, somatic symptoms, or even cognitive impairment. An additional challenge in dialysis patients is the overlap between dialysis- or kidney-failure-associated symptoms and those considered characteristic of depressive episodes (e.g., low appetite or fatigue). Nevertheless, depression should be considered in the differential diagnosis when patients present with functional decline, cognitive impairment, or nonadherence to therapy.

Screening for Depression

Several studies suggest that depression may be underrecognized and, based on these observations, screening is often recommended. In a large DOPPS study, fewer than 15% of patients had a diagnosis of depression made by the physician, while screening tests showed that actually more than 40% had scores suggestive of depression. Studies incorporating routine screening into clinical practice have been of only modest success, as often those at highest risk do not agree to participate in the screening process.

A variety of screening tools have been validated in the geriatric population. The Beck Depression Inventory (BDI) has been studied in dialysis patients but is lengthy. The Geriatric Depression Scale (GDS), which takes less time to administer, has also been used in dialysis patients. Both require adjusted cut-off values for determination of depression. A quick practical screening tool that is easily administered in the dialysis setting is the Personal Health Questionnaire-2 (PHQ-2). It is a sensitive, validated tool that is composed of two questions that ask patients about depressed mood or anhedonia. Patients' responses to each question are scored from 0 to 3 (in order of increasing severity). A score of 3 or higher prompts the health care provider to proceed with the PHQ-9, which can be used more reliably to diagnose depression. Both PHQ-2 and PHQ-9 have been studied in the dialysis population. The gold standard for the diagnosis of depression, however, remains psychiatric assessment and referral to a psychiatrist; ideally, one with expertise in the geriatric or kidney populations (or both) is recommended.

Management of Depression

Nonpharmacologic management of depression has been shown to benefit those who are able to participate. Group cognitive-behavioral therapy (CBT) and a modified bedside version of CBT have both been studied but require access to health care professionals trained to deliver such therapies. Group CBT can be difficult for in-center HD patients, who may be reluctant or find it challenging to travel routinely to the hospital on a nondialysis day. Bedside CBT has its own limitations, such as protection of privacy and more intensive resource use. Close collaboration with mental health

professionals with an interest in comanaging kidney patients may be helpful. Pharmacological interventions have also been used. Many commonly used antidepressants can, in fact, be prescribed to dialysis patients, albeit at reduced doses. Some may also have multifactorial benefits in terms of improved appetite (mirtazapine) or chronic pain management (duloxetine). The widest experience in the kidney failure population is with the use of sertraline, at doses of 50 to 100mg per day. Patients most commonly report gastrointestinal side effects with sertraline, but in elderly individuals, there are additional risks with antidepressants such as falls (see the Instability and Falls section), QT interval prolongation, and changes in suicidal ideation. In the dialysis population, both CBT and pharmacological treatments were equally associated with improvements in depression. Responses were at best modest, and there is still equipoise as to what the best treatment algorithm is. Recent clinical studies in the CKD population comparing the effect of pharmacological interventions on moderate to severe depression, versus placebo, have been disappointing. Unless nephrologists have comfort and experience overseeing this management on their own, usually comanagement with a psychiatrist is warranted.

Polypharmacy and Safe Prescribing

Polypharmacy has been traditionally defined as the use of four or more medications; however, in the dialysis setting, where the median number of pills taken every day by patients varies between 15 and 20, it has been suggested that the definition be adapted. Several adaptations have been proposed. The first, based on identifying those in the upper tertile of a typical U.S. dialysis population, suggests a cutoff of ≥ 14 medications as a practical definition for polypharmacy. An alternative method is to assess each patient individually at periodic intervals in collaboration with a pharmacist to identify unnecessary, unproven, or redundant medications. Key to safe prescribing is the need to routinely review medications, particularly around times of hospitalization and transition between specialists (see Recommended Reading).

Older individuals are particularly prone to medication-related events because of their accumulated comorbidity and concomitant cognitive and functional impairments (e.g., difficulty with pill bottles and/or blister packs because of decreased manual dexterity, grip strength, or vision and/or a failure to understand how to monitor and administer medications). The importance of medication timing in relation to meals, sleep, and dialysis schedules further add complexity such that phosphate binders, thyroid hormone replacements, statins, and antihypertensive drugs may be taken incorrectly and therefore be less effective. As a result, elderly dialysis patients are at particular risk of adverse drug events. Several drugs should not be routinely prescribed to geriatric patients. These include, among others, benzodiazepines, sedative-hypnotics, anticholinergic agents (e.g., dimenhydrinate and diphenhydramine), and alpha-blockers. (The American Geriatrics Society website carries an updated list of these medications.) Short-term opioid use may be indicated for acute events such as fractures or surgery; however, care should be taken to include a predetermined plan for down-titration and discontinuation. In particular, opioids, especially when co-prescribed with benzodiazepines, should be avoided. Recent dialysis literature has shown that the combination of these two drugs is associated with 1.5- to 2-fold higher mortality.

To reduce polypharmacy, it is important to recognize patients with limited longevity, functional or cognitive decline. These individuals may benefit from fewer drugs and modified clinical targets for blood pressure ($\leq 150/90$ mmHg) and glycemic control (hemoglobin A_{1c} [HbA_{1c}] $\leq 7.5\%$). Further details are available through the American Geriatric Society Guiding Principles for the Care of Older Adults with Multimorbidity. Medications should be reassessed after changes in health status or acute admissions. This limits drug interactions and reduces the inappropriate continuation of drugs with little long-term benefit or those that may result in low adherence. Collaboration with allied health team members, such as occupational therapists, can help to identify simple methods of improving adherence (e.g., alarms and other tools to remind patients of multiple medication administration times) or strategies to organize pills to minimize errors.

Instability and Falls

In a report published by the National ESRD Patient Safety Initiative in 2011, falls were identified as one of the top five safety issues for dialysis patients. In the general population, older age, medical comorbidities (e.g., malnutrition, diabetes, and cardiac disease), cognitive impairment or depression, and polypharmacy are all associated with a higher risk of falls. All of these risk factors exist in abundance in elderly dialysis patients. In addition, elderly dialysis patients are exposed to distinctive risks related to their kidney disease and uremia, as well as the dialysis process itself. CKD leads to a dysfunctional state of malnutrition with resistance to nutritional supplementation and subsequently results in protein-energy wasting and, in the extreme case, cachexia. Detailed studies of patients with CKD have shown that there are significant changes in both gait and body stability that likely increase the risk of falls. As CKD progresses, patients tend to have lower gait speed and shorter strides and spend more time with both feet touching the ground while walking. Some studies have found increased sway and decreased physical function immediately after dialysis when measured by such parameters as performance in sit-to-stand and gait initiation. Treatment with PD has a similarly increased fall risk to that seen with HD.

Falls, the inability to walk or transfer independently, and a reduction in gait speed are all predictive of higher risk of disability, as well as hospitalization and death. Injurious falls, such as those leading to hip fractures, are associated with

20%–50% higher 1-year mortality. In addition, individuals who have had an injurious fall in the year prior to starting dialysis appear to have a higher risk of subsequent falls, hospitalization, and/or admittance to long-term care. They have a lower chance of being waitlisted for transplantation, and of those who do undergo transplantation, prior falls are associated with a longer postoperative hospitalization and higher risk of graft failure. In patients maintained on dialysis, even noninjurious falls are associated with a higher risk of mortality, fear of falling, decreased independence, and a higher risk of admission to hospital or long-term care. Because of these sequelae, a fall, under most circumstances, should trigger updated discussions around prognosis, goals, and ACP.

Screening for Falls

A number of screening tools have been used to identify patients at high risk for falls. The Performance-Oriented Mobility Assessment (POMA), for example, is a comprehensive tool that is easily used with a minimum amount of training. Other published studies describe easy-to-use screening checklists that can be applied by any member of the care team. The 2010 Clinical Practice Guideline of the American and British Geriatrics Societies on falls prevention suggests a quick three-question screen for community-dwelling older patients, which can be used to identify those at higher risk of falls and who, therefore, might benefit from intervention.

1. Has the patient had two or more falls in the past 12 months?
2. Is the patient presenting with an acute fall?
3. Does the patient report any difficulty with walking or balance?

Individuals who answer yes to at least one of these questions should then undergo a more comprehensive, multidisciplinary assessment (e.g., with referral to a falls prevention clinic), including a home safety assessment (if applicable and available).

Treatment-Associated Factors That Impact Fall Risk

Fall risk modification requires a multidisciplinary, multiinterventional approach. Attention to other geriatric syndromes, such as depression or polypharmacy, can help minimize fall risk. In addition, there are several dialysis-related factors that may help reduce risk.

Physiological and Patient-Specific Risk Factors

Much of the fall risk associated with HD is attributed to postural changes pre- and postdialysis. Patients appear to have increased sway after HD, suggesting a relationship with subclinical postural hypotension. Unfortunately, no controlled trials of interventions used to mitigate orthostatic hypotension postdialysis have reported whether falls were less frequent. It would be reasonable, however, to pay attention to reducing this complication in high-risk dialysis patients, with careful and frequent dry weight assessments and screening for precipitating medications. Under some circumstances, it may be valid to permit a moderate degree of edema or to target blood pressure goals to standing blood pressure readings.

Electrolyte abnormalities, such as hyponatremia, can contribute to falling risk. Anemia and metabolic acidosis both affect strength and muscle mass and thus, might contribute to a higher risk of falls and fractures. Careful attention to these parameters during routine dialysis rounds might be helpful in patients for whom falls screening is positive. Dialysis patients also face unique challenges in terms of muscular dysfunction and mineral and bone disorders associated with bone disease. Patients with adynamic bone disease may experience generalized body aches and muscle weakness, while those with hyperparathyroidism are at risk of spontaneous fractures and gait disturbances arising from these. Current recommendations from the National Institute of Health (March 2020) no longer recommend vitamin D supplementation in the older general population. Unfortunately, given the complicated nature of the calcium–phosphate axis, bone disease with kidney failure in dialysis patients, and the absence of evidence specific to this population, it is not clear whether vitamin D supplementation is beneficial in mitigating fall risk in the dialysis population. Additionally, risks associated with adding more medications to patients at risk of polypharmacy must also be considered.

Efforts should be made to optimize polypharmacy and withdraw psychotropic medications (or at least reduce their doses) (see the Polypharmacy and Safe Prescribing section). There is some evidence that visual impairment is more prevalent in elderly dialysis patients than in the general population. Although there is no evidence specifically in the kidney failure population, expediting first cataract surgery for patients in whom it is indicated is recommended by the American Geriatric Society/British Geriatric Society (AGS/BGS) guidelines as part of a multifactorial intervention in high-risk patients (see next section).

Environmental Risks Within the Dialysis Unit

The dialysis unit itself presents opportunities for decreasing fall risk. Design and efficient use of the unit to minimize clutter and obstacles between dialysis machines and stations, doorways, scales, and so on may be helpful. Other environmental hazards include spills or leakages on floors, poor lighting, and the scales used to weigh patients pre and postdialysis. Published experiences suggest that it may be helpful to have staff assistance in transfers, ambulation, and weighing for patients who are identified as being high risk for falls and that root cause analysis or other quality improvement methodologies may be effective to minimize an individual dialysis unit's environmental risks for falls.

Multifactorial Management of Falls

Multifactorial management is the cornerstone of fall risk reduction. In addition to the strategies described earlier, exercise programs that include strength training, gait and balance, and coordination training seem to be effective in fall risk reduction. Activities such as tai chi, endurance

training, and flexibility exercises are suitable for frail seniors who wish to reduce fall risk. The AGS/BGS guidelines suggest that programs last a minimum of 12 weeks and involve one to three sessions per week. Home assessments and modifications implemented by trained health care professionals, such as occupational therapists, are also helpful as part of multifactorial management programs, as are programs that assess and correct issues related to the feet (e.g., ulcers, nails, or other deformities) and footwear. Unfortunately, it is less clear if any of the previously mentioned strategies are effective in older patients with cognitive impairment.

Nondialytic Management and Comprehensive Conservative Kidney Care

There is an emerging body of evidence that suggests that nondialysis care (or Comprehensive Conservative Kidney Care) may have similar survival outcomes to those seen after initiation of dialysis for older, frail patients. This has fewer negative effects on functional dependence and quality of life, particularly in elderly kidney failure patients with significant medical comorbidities, dementia, and/or poor functional status or those requiring skilled nursing support. It is important to include a discussion about comprehensive conservative kidney care for all patients. Universal access to dialysis has led to it often being a default pathway for kidney failure to the detriment of some patients. In some, the better survival associated with dialysis initiation is counterbalanced by a markedly fewer number of hospital-free days. Most comparisons, however, are for in-center HD, with little comparison for PD or home HD.

Most experts suggest comprehensive conservative kidney care be provided by a dedicated team who follow patients prospectively. Patients and families need to be reassured that they will continue to be cared for and, as the patient progresses toward death, given information about how or where to get support at any time. Symptom burden in kidney failure patients, whether they are on dialysis or not, is high. The most commonly reported symptoms include low energy, pruritus, dyspnea, constipation or nausea, and pain. In stage 5 CKD patients managed without dialysis, there is some evidence that symptom burden increases significantly, along with a precipitous functional decline in the last 1 to 2 months of life. Early comanagement with palliative care teams, particularly those with expertise with patients who have nonmalignant diseases or chronic organ failure, may be useful. Further research is needed to demonstrate whether this may, in fact, confer better survival, specifically in CKD/kidney failure patients, as has been shown with other patient populations.

Palliative Dialysis and Dialysis Discontinuation

Palliative dialysis is a term applied to dialysis care that prioritizes the management of patient symptoms and well-being over interventions that are known to have evidence of benefit but may indirectly impact patient well-being. In this context, dialysis can either be adjusted with a focus on symptom management (e.g., used as needed to treat dyspnea due to volume overload) or adapted, keeping in mind the patient's preferences or goals. Changes may involve modifying the schedule of dialysis, its location, or frequency to allow patients to participate in their chosen activity. Relaxation of dietary restrictions and adaptation of biochemical targets may be appropriate. Each scenario should ideally be discussed as a part of ACP and addressed with adequate time to avoid decision-making in a reactive or crisis-driven manner. Expected survival with palliative dialysis is difficult to define and is variable according to each patient.

Understanding dialysis as a choice encompasses the possibility of adjusting or discontinuing dialysis as part of a shared decision-making process. Patients with significant symptom burden with dialysis treatment, multiple comorbidities, or functional decline have a limited life expectancy and may eventually reach a health status where they prefer to discontinue dialysis. Cultural and societal values seem to play a large role in the reasons for dialysis discontinuation, and rates vary widely across the world. As with other areas of ACP, cultural differences need to be incorporated into decisions about dialysis discontinuation, particularly as physician attitude and program processes impact discontinuation. Decision-making capacity needs to be defined, understanding that patients with cognitive impairment or depression may still retain capacity for decision making.

Patients deciding to discontinue dialysis benefit from a multidisciplinary approach, and involvement of palliative and spiritual care support are definitely warranted. Survival after discontinuation spans in the range of a few days to a couple of weeks, depending on residual kidney function and nutrition, with a median observed survival between 7 and 10 days after the last treatment. Patients and their caregivers should be taught about the possible trajectories when approaching the end of life and given information about final hours and days. Information should include the appearance of progressive drowsiness from uremic encephalopathy or sedation related to medications used to treat symptoms, dyspnea due to acidemia or volume overload, and cardiac asystole due to hyperkalemia. There is evidence that preparing caregivers for this situation and helping through the bereavement process reduces posttraumatic stress, anxiety, and feelings of guilt.

Goal Setting and Advance Care Planning

Goals of care are increasingly an important part of quality clinical care. Goals should be constantly reviewed, modified if necessary, and treatments adapted to the immediate needs of patients. ACP, in contrast, is a dynamic process with a focus on future health. ACP discussions allow patients, their families or loved ones, and their health care teams to explore how the patients' goals, values, beliefs, and understanding of their illness interact with future medical decisions as health

declines. ACP includes but is not limited to the development of advanced directives, decisions around resuscitation, and identification and education of the substitute decision-maker. Both Goals of Care and ACP discussions should be revisited whenever a patient's health status changes, after hospitalization, or after he or she experiences an acute event. In a randomized trial of elderly patients without CKD, ACP significantly improved care at the end of life because patients' prior wishes were more likely to be known and respected.

Substitute Decision Makers

It is particularly important to identify and engage one or more individuals willing to take on the role of a substitute decision-maker early on in the process of ACP. A significant proportion of elderly dialysis patients are no longer capable near the end of life, given the illness burden and significant risk of cognitive impairment in this population, and substitute decision-makers are then asked to make decisions on their behalf. Research in the general population, however, has consistently shown that substitute decision-makers and health care professionals do little better than chance alone (if even that well) in predicting what patients' wishes would be unless they have participated frequently in discussions along the health trajectory. Advance directives have been shown to improve the likelihood that patients will receive the care that they want. They have also been shown to alleviate the anxiety, depression, and other psychological or emotional sufferings that substitute decision-makers may feel in making such difficult decisions on behalf of patients. Engaging substitute decision-makers early on in the ACP process helps to strengthen their relationships with patients and health care teams and to reassure them when the time comes for them to enact their role that they can do so with prior understanding of what their loved one would want.

Gathering Information for Advance Care Planning Discussions

ACP is particularly important in elderly dialysis patients, as they have a limited life expectancy compared with nondialysis age- and gender-matched control participants or younger fellow dialysis patients. ACP discussions should include information about both prognosis and the most likely disease trajectory, including a frank discussion about complications arising from the high incidence of falls and cognitive or functional changes. Several methods are available for prognostication, but as a rough guide, life expectancy at the time of dialysis initiation is approximately reduced by two-thirds when a patient reaches the point where dialysis is indicated. In 2015, for example, prevalent dialysis patients in the United States aged 75 to 79 years had an expected remaining lifetime of 3.5 compared with 10.6 years in the general population in that age group; in patients between the ages of 80 and 84 years, this dropped to 2.9 versus 7.8 years. Additionally, a number of online prognostic tools and calculators are available to help estimate 3-, 6-, or 12-month mortality after dialysis initiation. Examples of clinical factors important to prognostication include increased age, low serum albumin, answering "no" to the surprise question, medical comorbidities (especially ischemic heart disease, dementia, or peripheral vascular disease), functional dependence before starting dialysis, a low body mass index, and sentinel events (e.g., amputation or myocardial infarction). Caution should be used as these tools are not intended to be used to withhold dialysis from selected patients but rather to help guide the decision-making process around management options as kidney failure approaches.

Uncertainty and Advance Care Planning Discussions

The vast majority of U.S. dialysis patients have not completed ACP discussions at the time of death. Even in those who have had ACP discussions, dialysis patients are less likely to complete directives limiting aggressive measures at the end of life. This lies contrary to evidence that supports lower hospitalization rates, invasive procedures, and intensive care unit (ICU) admissions at the end of life and higher rates of hospice use and dialysis discontinuation in those in whom ACP is addressed appropriately. Compared with patients with heart failure or cancer, elderly dialysis patients spend more days in the hospital and ICU, are more likely to undergo invasive procedures, and are less likely to die in a hospice setting in the last month of life. Although the willingness of patients and families to discuss prognosis depends not only on individual experiences and preferences but also on cultural background, there are several studies that indicate that nephrologists usually underestimate patients' desire to discuss prognosis and ACP. As a result, discussions about expected survival and illness trajectory in kidney failure or dialysis are rare. The result is a systematic gap in care that can negatively affect patients' and families' awareness of what they can expect as the illness progresses and alleviation of their symptoms and emotional suffering. Published experiences where ACP is incorporated into routine nephrology care show the importance of formalized training programs for dialysis teams, dedicated clinics for discussions around ACP, and dedicated team members to facilitate these discussions. A number of structured guides may be used to help with these discussions. These include, among others, the Serious Illness Conversations Guide or VitalTalk (both available online). Nephrologists often identify that the biggest barrier to holding discussions about goals of care is the uncertainty around an individual patient's prognosis or disease course. Uncertainty can be conveyed to patients and families using the "Best Case, Worst Case" discussion (see Recommended Reading). This allows recognition of the uncertainty but places emphasis on the likely outcomes and sets more appropriate expectations.

Conclusion

Elderly patients initiating dialysis are at higher risk of geriatric syndromic illnesses, such as functional decline, falls, and cognitive impairment. The high morbidity and mortality

associated with these illnesses warrant a unique and personalized approach both to dialysis care and to overall care. Open discussions of expectations, prognosis, and ACP are recommended and may allow the clinician to adapt goals of dialysis care to the individual.

Recommended Reading

Farragher J, Einbinder Y, Oliver MJ, Nachman J, Chow E, Jassal SV. Importance of early inpatient geriatric rehabilitation on outcomes in individuals on dialysis. *Arch Phys Med Rehabil.* 2020;101:227–233.

Research paper on the benefits of a geriatric rehabilitation program after dialysis initiation.

Grubbs V. Time to recast our approach for older patients with ESRD: the best, the worst, and the most likely. *Am J Kid Dis.* 2018;71(5):605–607.

A good description of when and how to use the best case vs. worst case scenario when there is uncertainty about prognosis.

Hall RK, McAdams-DeMarco MA. Breaking the cycle of functional decline in older dialysis patients. *Semin Dial.* 2018;31:462–467.

Excellent summary of risk factors for functional decline in dialysis patients and the benefits of a comprehensive geriatric assessment to identify modifiable factors.

Jassal SV, Farragher JF. MoCA: turn your mind to it. *J Am Soc Nephrol.* 2020;31:627–623.

Brief and useful editorial on the benefits of cognitive evaluation in ESKD patients and usefulness of the MoCA.

Kurella Tamura M, Monte-Rath ME, Hall YN, Katz R, O'Hare AM. Advance directives and end-of-life care among nursing home residents receiving maintenance dialysis. *Clin J Am Soc Nephrol.* 2017;12:435–442.

Review of USRDS data on advanced directives from dialysis patients living in nursing homes.

Kurella Tamura M, O'Hare AM, Lin E, Holdsworth LM, Malcolm E, Moss AH. Palliative care disincentives in CKD: changing policy to improve CKD care. *Am J Kidney Dis.* 2018;71(6):866–873.

Informative review listing many limitations of trying to appropriately provide palliative care to dialysis populations.

MacPhail A, Ibrahim JE, Fetherstonhaugh D, Levidiotis V. The overuse, underuse, and misuse of dialysis in ESKD patients with dementia. *Semin Dial.* 2015;28(5):490–496.

A balanced review highlighting how patients with cognitive impairment are at risk of having either over- or underuse of dialysis.

St. Peter, WL. Management of polypharmacy in dialysis patients. *Semin Dial.* 2015;28(4):427–432.

A great review on polypharmacy in dialysis patients, introducing improved definitions for the concept and describing measures to improve it.

Vandecasteele SJ, Kurella Tamura MA. Patient-centered vision of care for ESRD: dialysis as a bridging treatment or as a final destination? *J Am Soc Nephrol.* 2014;25(8):1647–1651.

A paper proposing a new approach to the management of patients starting dialysis therapies based on their expected survival and morbidity outcomes. This paper introduces the idea of a more symptom-focused approach in patients who are expected to continue regular chronic dialysis sessions until nearing the time of death in comparison to those maintained on dialysis as a bridge to transplantation or renal recovery.

Walker SR, Wagner M, Tangri N. Chronic kidney disease, frailty, and unsuccessful aging: a review. *J Ren Nutr.* 2014;24(6):364–370.

An excellent review on the concept of frailty and its role in the renal literature.

Wolfgram DF. Intradialytic cerebral hypoperfusion as mechanism for cognitive impairment in patients on hemodialysis. *J Am Soc Nephrol.* 2019;30:2052–2058.

Excellent review of vascular changes in HD, mechanisms for cognitive impairment in HD, and available imaging techniques for evaluation.

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Liver Disease and Gastrointestinal Disorders in Dialysis Patients

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Introduction

Patients with end-stage kidney disease on maintenance dialysis show a variety of acute and chronic diseases of the liver. Viral hepatitis continues to be the most frequently recognized cause of liver damage in patients on regular dialysis; the most important causes of hepatitis in this population remain chronic hepatitis B and C infection (Table 51.1). The majority of the literature on liver disorders in the dialysis population regards patients on hemodialysis (HD). Patients receiving peritoneal dialysis are at lower risk for acquisition of blood-borne infections for several reasons; the absence of extracorporeal blood manipulation; it is performed in the patient's home, where there is no exposure to pathogens from other patients, and there is a decreased likelihood of blood transfusions among patients undergoing peritoneal dialysis.

The most important causes of death in patients on maintenance dialysis remain cardiovascular diseases and infections; cirrhosis and hepatocellular carcinoma (HCC), two major complications related to chronic viral hepatitis, are uncommon among patients on intermittent dialysis. A large Asian registry based on patients with HCC does not frequently list end-stage kidney disease on maintenance dialysis (1.2%) as a comorbid condition. Although there was no significant difference in the comparison of long-term survival between HCC patients receiving dialysis and those who do not, hepatitis B and C infections were much more prevalent in dialysis patients with HCC than the entire HCC population.

Hepatitis B

Hepatitis B virus (HBV) is a partially double-stranded compact DNA virus that is spread by intimate and nonintimate contact as well as parenterally. The most common modes of transmission of HBV in the adult population in the developed world are sexual contact and intravenous drug use; maternal-to-infant transmission is an important mode of transmission in endemic areas such as Asia and sub-Saharan Africa.

Interpretation of Diagnostic Tests

Hepatitis B surface antigen (HBsAg) is the first marker of HBV detectable in serum in acute infection. By the time clinical and biochemical hepatitis is present after an incubation period of up to 140 days, other serologic markers of HBV infection appear, including antibody to HBV core antigen (anti-HBc). Hepatitis B core antigen, a marker of viral replication found in infected hepatocytes, does not circulate in serum. However, its corresponding antibody (anti-HBc) does. Documented HBsAg positivity in serum for 6 months or more suggests chronic HBV with a low likelihood of subsequent spontaneous resolution. Chronic HBV is diagnosed by the absence of immunoglobulin M (IgM) anti-HBc antibody. IgM anti-HBc antibody is a marker of acute or recent acute hepatitis B and is detectable for 6 months after infection, whereas IgG anti-HBc is lifelong. If acute HBV resolves, neutralizing antibody against HBsAg (anti-HBs) develops. If HBV infection becomes chronic, other HBV markers—including HBV viremia (HBV DNA) and hepatitis E antigen (HBeAg)—should be sought. Both of these markers imply viral replication and, thus, greater infectivity, although any patient who is HBsAg positive is potentially infectious.

Natural History of Hepatitis B Virus in the Dialysis Population

The course of HBV infections is frequently asymptomatic and indolent among patients on maintenance dialysis; some symptoms that typically occur in nondialysis patients with HBV (i.e., asthenia, fatigue, and cognitive impairment) are common in the dialysis population irrespective of their HBsAg serologic status. Evaluation of the seriousness of HBV infection in patients on long-

TABLE 51.1 Liver Disease in Dialysis Patients

Acute viral hepatitis: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV)
Chronic viral hepatitis: hepatitis B virus (HBV), hepatitis C virus (HCV)
NASH: nonalcoholic steatohepatitis
Drug hepatoxicity
Iron overload
Congestive heart failure

term dialysis is hampered by the observation that serum aminotransferase levels are commonly lower in patients on dialysis or with predialysis chronic kidney disease than among individuals with intact kidney function. No marked elevations of liver enzymes have been observed, but serum aminotransferase and gamma-glutamyl transpeptidase are frequently greater in HBsAg-positive than HBsAg-negative individuals on long-term dialysis. In contrast to renal transplant recipients with chronic HBV infection, there is no evidence of accelerated progression to decompensated cirrhosis or HCC.

Mortality is an unequivocal endpoint in the natural history of HBV, but data concerning the relationship between HBV infection and risk for death among HBV-infected patients on long-term dialysis are not abundant. One survey from financially constrained dialysis facilities has shown that the death rate was greater among HBsAg-seropositive than HBsAg-seronegative patients undergoing long-term dialysis. Liver failure was more common in HBsAg-seropositive than HBsAg-seronegative patients. These investigators concluded that the clinical outcomes of renal replacement therapy are apt to be adversely affected by inadequate dialysis or infections due to limited financial resources.

Epidemiology of Hepatitis B Virus in Dialysis Facilities

Soon after the discovery of HBV (late 1960s), hepatitis B was recognized as an important threat for staff and patients within dialysis facilities. In 1977, the Centers for Disease Control and Prevention (CDC) issued isolation guidelines to prevent the transmission of HBV within dialysis facilities. In addition to the CDC recommendations, the screening of blood products for HBsAg and anti-HBc antibody and a lower need for blood products resulted in a fall in the incidence and prevalence of HBV among patients and staff within dialysis facilities from North America and western Europe during the period 1974 to 1995. The most recent and large (n = 263,820) survey on the epidemiology of HBV among patients undergoing long-term dialysis in the developed world remains the 2002 survey by the CDC. It reported a 1.0% mean prevalence of HBsAg-seropositive patients; the incidence of HBV infection was 0.12%. HBV appears more common in many low-income countries where the rate of patients on maintenance dialysis who are chronic HBsAg carriers ranges between 1% and 15%.

The delivery of health care in the developed world has changed over recent years, leading to an increased number of patients treated outside of acute care hospitals. Thus, numerous outbreaks of HBV infection in nonhospital health care settings, including dialysis facilities, have been reported. Lack of compliance to standard and dialysis-specific infection control precautions is likely the most important cause of patient-to-patient transmission of HBV in dialysis facilities, according to a recent systematic review of reports on outbreaks.

Strategies to Control Hepatitis B Virus Transmission in Dialysis Facilities

To prevent the transmission of blood-borne pathogen agents in general health care settings, “universal precautions” have been recommended by the CDC. These procedures are now referred to as “standard precautions” and include (1) handwashing after touching blood and other potentially infectious material, (2) wearing of gloves when touching blood or other potentially infectious material, and (3) use of gowns and face shields when exposure to blood or body fluids has been anticipated.

In addition to these "standard precautions," there are routine HD facility precautions that are unique to the HD setting and are more stringent than the “universal precautions.” The infection control practices specific to the HD environment recommend that glove use is necessary whenever patients or HD equipment is touched and that there should be no sharing of supplies, instruments, or medications between HD patients, including ancillary supply equipment (trays, blood pressure cuffs, clamps, scissors, and other nondisposable items). Further, HD center precautions specify the separation of clean areas (used for handwashing and handling and storage of medications) from contaminated areas (handling blood samples and HD equipment after use) and cleaning and disinfection of nondisposable items, machines, and environmental surfaces between uses. In addition, other precautions to prevent HBV acquisition in the HD environment are needed: monthly serologic testing for HBsAg of all susceptible patients, prompt review of results, physical separation of HBsAg-positive from susceptible patients, and cohorting of separate dialysis staff, instruments, supplies, and HD machines to patients with HBsAg positivity.

Treatment of Hepatitis B Virus–Related Liver Disease

Several drugs have received approval for the treatment of chronic HBV infection, including conventional or pegylated interferons, the nucleoside analogues lamivudine and telbivudine, and the nucleotide analogues entecavir, adefovir, tenofovir disoproxil, and tenofovir alafenamide. Antiviral therapy is recommended in HBsAg-positive patients with active viral replication, HBeAg-positive status, and elevated alanine aminotransferase (ALT) levels. Clearance of HBsAg with anti-HBs seroconversion is an important aim of treatment for all HBV therapies. However, this goal can be reached in only a small proportion of immunocompetent patients, and reaching this goal is likely to be even less common in immunocompromised patients such as those on HD. Clearance of HBeAg and loss of HBsAg, indicating complete resolution of HBV infection, are more commonly obtained with interferons than with nucleos(t)ide analogues (NUCs). The ultimate goal for treatment of chronic HBV is to prevent the development of irreversible complications such as cirrhosis, liver failure, and hepatic cancer.

The evidence in the literature on antiviral therapy of chronic HBV in dialysis patients is very limited: the low rate of HBsAg-positive patients undergoing intermittent dialysis in the developed world clearly hampers the implementation of randomized or cohort clinical trials in this area. The information available on this point mostly relies on lamivudine. Small and uncontrolled prospective clinical studies have shown that lamivudine is effective and safe for HBV in many dialysis patients: treatment results in normalization of ALT values and persistent clearance of HBV DNA. A major limitation of lamivudine is its high rate of viral resistance. Although the data on the use of other NUCs for HBV in the dialysis population remain anecdotal, there are some studies confirming entecavir efficacy in this population.

According to international guidelines on HBV treatment, entecavir and tenofovir disoproxil or alafenamide are the first NUCs of choice over the others previously mentioned, given they have a reduced risk of drug resistance and greater efficacy compared with older agents. Doses need to be adjusted for patients on dialysis (Table 51.2).

Hepatitis B Vaccination

Hepatitis B vaccination has been recommended for all seronegative dialysis patients and staff members since the early 1980s. Safe and effective vaccines that contain HBsAg, either plasma derived or manufactured by recombinant DNA technology, are currently available. However, the fall in the incidence of HBV infection within dialysis facilities of developed countries (between 1976 and 1980) antedated the availability of the HBV vaccine. Patients on maintenance dialysis show cellular immunodeficiency that impairs not only the clearance of HBV but also the immunoresponsiveness to HBV vaccine—the frequency of responders (i.e., patients developing anti-HBs titers with protective concentration) is lower than in the general population. Moreover, after completion of the vaccination schedule, the antibody titers of responder dialysis patients are low and fall rapidly. Various approaches have been adopted to overcome the nonresponsiveness of chronic uremic patients: intramuscular administration of multiple or double doses; coadministration of zinc or immune modulators such as levamisole, thymopentin, interleukin-2, and gamma-interferon; and intradermal administration of HBV vaccine. Despite these attempts, the proportion of nonresponders (patients who are not able to develop anti-HBs concentration above the protective level of 10 mIU/mL after HBV vaccine) remains higher among dialysis patients. Currently, a 0-, 1-, 2-, and 6-month schedule with double doses of HBsAg (2 × 20 μg HBsAg) of recombinant hepatitis B vaccine by the intramuscular route (deltoid muscle) is recommended in dialysis patients, with regular monitoring of antibody levels and administration of one booster dose whenever antibody titers decline below the protective concentration. In order to improve the immunogenicity of recombinant hepatitis B vaccines, var-

TABLE 51.2 First-Line Nucleoside Analogues in HBV Treatment: Adjusted Doses According to Kidney Function

Creatinine Clearance (mL/min)	Naive ETV (mg/24 h)	ETV LAM-R (mg/24 h)	TDF	TAF*
> 50	0.5	1	300 mg/24 h	
30–49	0.25	0.5	300 mg/48 h	
10–29	0.15	0.3	300 mg/72–96 h	
Dialysis	0.05	0.1	300 mg/week	

*No dosage adjustment of TAF is required in patients with mild, moderate, or severe kidney impairment (creatinine clearance > 15 mL/min) or in patients with end-stage kidney disease (creatinine clearance < 15 mL/min) on long-term hemodialysis. On days of hemodialysis, we suggest administering TAF at the end of the hemodialysis session. TAF is not recommended in patients with end-stage renal disease who are not hemodialysis dependent.
ETV; Entecavir; *LAM-R*, lamivudine resistant; *HBV*, hepatitis B virus; *TDF*, tenofovir disoproxil; *TAF*, tenofovir alafenamide.

ious adjuvant systems have been recently developed, and one of them (AS04) appears to give encouraging results in terms of efficacy and safety, according to some randomized controlled trials. Studies in unselected cohorts of patients on maintenance dialysis are underway to confirm these findings.

Hepatitis C

Hepatitis C virus (HCV) is a single-stranded RNA virus. The route of contamination by HCV is almost entirely parenteral, making HCV significantly less infectious than HBV. Prior to the 1990s, the main routes of transmission were blood product transfusion, intravenous drug use, or unsafe injection procedures. Since the systematic screening of blood products, the residual risk of transfusion-related HCV infection is extremely low (around 1/2,000,000). In industrialized countries, important routes of transmission remain intravenous or nasal drug use, mother-to-child transmission, and unsafe medical or surgical procedures. The risk of heterosexual transmission is currently low but high in HIV-positive men who have sex with other men. It has been calculated that around 30% of cases of HCV infection are still unexplained, and occasional transmission has been observed with acupuncture or tattoos. The risk related to dialysis is 1%–2% per year, and it varies in different countries.

Interpretation of Diagnostic Tests

The diagnosis of HCV infection is based on the detection of anti-HCV antibodies by third-generation enzyme-linked immunosorbent assays (ELISAs). Anti-HCV-positive patients need to be tested for HCV viremia (HCV RNA) in serum by polymerase chain reaction (PCR) techniques; patients with active HCV infection are anti-HCV positive, HCV RNA-positive, whereas HCV RNA-negative patients have inactive HCV infection. A small but significant minority of anti-HCV-negative patients on regular dialysis show detectable HCV RNA in serum; this implies that HCV RNA testing should be done if there is concern about HCV infection despite negative serologies. A variety of HCV RNA tests for HCV are available; quantitative tests measuring HCV viral load (HCV RNA) with a lower limit of detection of 6–15 IU/mL are recommended. Qualitative tests are no longer in use.

Natural History of Hepatitis C Virus in Dialysis Patients

The long-term consequences of HCV infection are difficult to assess among patients on long-term dialysis for several reasons. HCV infection is usually asymptomatic, with an apparently indolent course, the natural history of HCV extending over decades rather than the years, and the adverse consequences of chronic HCV infection may not be obvious in individuals followed for short periods of time, such as dialysis patients. Patients undergoing maintenance dialysis have a shortened life expectancy because their average age is high, and they have a large number of comorbidities. The recent implementation of guidelines recommending antiviral therapy for HCV infection in the dialysis population makes it difficult to conduct longitudinal clinical trials on the natural history of HCV infection in patients on long-term dialysis. Clinicians are usually reluctant to perform a liver biopsy in dialysis patients because of the risk of bleeding related to platelet dysfunction due to uremia.

An updated meta-analysis of 15 observational studies (n = 195,370 unique patients) about the effect of anti-HCV serologic status on survival in dialysis patients documented an independent and significant impact of HCV on mortality among individuals receiving long-term dialysis. The adjusted relative risk (all-cause mortality) was 32% higher in anti-HCV-positive patients on maintenance dialysis. Various mechanisms support the excess death risk of HCV-infected patients, in addition to liver-related mortality. There was an increased risk of cardiovascular mortality among HCV-infected patients, and this has been associated in part with malnutrition and chronic inflammation. An impairment of health-related quality of life has also been documented.

Epidemiology of Hepatitis C Virus in Dialysis Facilities

A high prevalence of HCV among patients receiving long-term dialysis has been observed in the early 1990s, but the universal introduction of sensitive tests for screening blood products, as well as the widespread availability of erythropoiesis-stimulating agents and the compliance with infection control procedures, have helped to reduce the prevalence of HCV among patients on maintenance dialysis in the developed world. The prevalence of HCV in dialysis patients currently ranges from below 5% in northern Europe, around 10% in southern Europe and the United States, and between 10% and 70% in developing countries (including North Africa, Asia, and South America). The prevalence of HCV is highly variable from facility to facility within the same country, with recent reports from some dialysis facilities in the United States still showing prevalences of 25%–30%. Nosocomial transmission is now the most likely source when patients on regular HD in industrialized countries develop anti-HCV antibodies. The nosocomial spread of HCV among patients on long-term dialysis has been supported by several epidemiologic findings and confirmed in studies based on molecular virology. In fact, portions of the HCV genome are greatly variable and lend themselves to fingerprinting of each strain using nucleic acid testing (NAT) and sequencing. This strategy is analogous to the sequencing of the V3 region used in studies on human immunodeficiency virus (HIV) transmission.

Strategies to Control Hepatitis C Virus Transmission in Dialysis Facilities

The most important mechanism in nosocomial transmission of HCV among patients receiving long-term HD is currently suboptimal adherence to infection control procedures against blood-borne pathogens. These include "universal precautions" and other precautions specific to the HD setting, as reported earlier. Unlike the procedures for HBV, additional HD precautions (physical separation of HCV-positive from HCV-negative patients) and the cohorting of separate dialysis machines, instruments, supplies, and staff to HCV-infected patients are not recommended in various clinical guidelines (CDC and Kidney Disease: Improving Global Outcomes [KDIGO]). In fact, large prospective studies have not identified isolation of HCV-infected HD patients as an effective measure to reduce nosocomial HCV transmission. The use of dedicated dialysis machines for HCV-infected patients also is not indicated. It has been suggested that monthly monitoring of serum aminotransferase levels and periodic retesting for anti-HCV antibodies in patients on HD who test negative for HCV be done routinely. Quarterly monitoring of serum aminotransferase levels in patients on peritoneal dialysis is also recommended.

Another way to reduce transmission is by treating all patients with the new direct-acting antivirals (DAAs). This strategy is called the microelimination of HCV. Once HCV is cleared, avoiding reinfection is of utmost importance.

Therapy of Hepatitis C Virus in Dialysis Patients

The treatment of HCV in patients on chronic dialysis is predicated on the premise that HCV is associated with decreased patient survival. However, recent evidence supports the view that HCV-infected patients on intermittent dialysis very rarely receive antiviral therapy; this is probably related to several factors, including concerns about side effects with pegylated interferon and ribavirin and the need of experienced clinicians to give antiviral therapy, among others. The KDIGO HCV Study Group recommends the antiviral treatment of all HCV-infected patients on the waiting list for a renal transplant, irrespective of whether they are dialysis dependent or not. Monotherapy with PEG-interferon with or without ribavirin had been considered over the past decades as the mainstay of antiviral therapy of chronic hepatitis C in patients receiving long-term dialysis. Tolerance to interferon appears to be lower in dialysis than in nonuremic patients with chronic HCV infection. However, 30%–80% of dialysis patients with HCV have been successfully treated with sustained clearance of circulating HCV RNA.

A better understanding of the viral cycle of HCV and characterization of viral enzymes that are potential targets have resulted in the development of new molecules, DAA drugs targeted against HCV, either specific of genotype 1 (NS3/NS4A protease inhibitors and NS5 polymerase inhibitors) or with a wider spectrum (NS5A or entry inhibitors) (Table 51.3).

Ledipasvir, daclatasvir, velpatasvir, voxilaprevir, and the combination ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir (also known as ProD or 3D regimen), as well as grazoprevir/elbasvir and glecaprevir/pibrentasvir, have hepatic metabolism and can be used in patients with advanced kidney disease (estimated glomerular filtration rate [eGFR] < 30 mL/min) and in patients on dialysis. Sofosbuvir, given its renal metabolism, was not recommended for administration to patients with an eGFR < 30 mL/min or those on dialysis. Recent studies suggest that sofosbuvir can be used safely in this population and clinical trials are underway.

Thus, treatment of chronic hepatitis C has evolved considerably in the past decade. No new drugs are expected to be approved for HCV treatment, and current available DAAs are enough to cover all HCV treatment needs in dialysis patients. A large debate about treating some patients while on dialysis or after kidney transplantation exists. The approval of sofosbuvir use in dialysis patients will change this point, and updated recommendations will be needed. In the meantime, treatment decisions should be based on patient benefits.

TABLE 51.3 Current Available Hepatitis C Antiviral Drugs: Direct-Acting Antiviral Agents

Protease Inhibitors	NS5A Inhibitors	Polymerase Inhibitors (NUCs)	Polymerase Inhibitors (Non-NUCs)
Paritaprevir	Daclatasvir	Sofosbuvir	Deleobuvir
Grazoprevir	Ledipasvir		Dasabuvir
Glecaprevir	Ombitasvir		
Voxilaprevir	Elbasvir		
Paritaprevir	Velpatasvir		
	Pibrentasvir		

NUC, Nucleos(t)ide analogue.

Nephrogenic Ascites and Other Gastrointestinal Disorders in the Dialysis Population

Gastrointestinal (GI) disorders are common among patients on regular dialysis, with almost 80% of dialysis patients reporting dyspepsia or other symptoms of GI distress. Some nonspecific GI symptoms, including nausea, vomiting, anorexia, metallic taste, or loss of taste, were commonly encountered in the past as they mirror advanced uremia. These symptoms can still be seen in patients where dialysis is delayed or not available. Their presence can be useful in order to evaluate dialysis adequacy or the time to start renal replacement therapy.

Dyspepsia is characterized by nausea, vomiting, upper abdominal pain or bloating, and early satiety; it has been frequently associated with delayed gastric emptying. Early satiety or poor appetite could be caused by gastroparesis even in the absence of overt problems such as nausea and vomiting. Gastroparesis is better recognized in diabetics; however, it is common in all-cause end-stage kidney disease, varying between 36% and 62% among patients on chronic dialysis. Various mechanisms have been suggested in the pathogenesis of delayed gastric emptying, including peritoneal dialysate volume, prolonged postprandial suppression of ghrelin secretion, and uremic autonomic neuropathy despite seemingly adequate dialytic therapy. The symptoms of gastroparesis may negatively impact nutritional status and decrease quality of life among patients on maintenance dialysis. Pharmacological interventions such as prokinetics and antiemetic drugs or nonpharmacologic interventions (i.e., gastric surgery and gastric electrical stimulation) have not been conclusively proven to be effective and safe.

It is well known that an increased rate of upper (such as gastritis and gastroparesis) and lower (diverticular disease and colonic perforation) GI disorders occur in the dialysis population compared with nonuremic patients. Chronic kidney disease has been previously associated with an increased frequency of peptic ulcer disease among patients receiving long-term dialysis, but endoscopic studies have shown that peptic ulcer disease is no more common in dialysis patients than in nondialysis patients. *Helicobacter pylori* have a close association with the development of peptic ulcers, gastric cancer, and gastric lymphoma; it has been considered one of the major risk factors for GI symptoms among patients on intermittent dialysis. Recent consensus shows that the prevalence of *H. pylori* in dialysis patients is significantly lower than in subjects with intact kidneys.

HD patients carry a higher risk of peptic ulcer bleeding, and recent data have shown a higher risk of nonpeptic, nonvariceal GI bleeding in HD patients after adjustments for age, gender, underlying comorbidities, and ulcerogenic medications.

A number of studies have addressed the prevalence of biliary lithiasis in HD patients, with inconsistent results. Some investigators have found prevalence rates similar to those observed in the local general population; others have found a greater prevalence among patients receiving long-term dialysis. According to a large and recent survey from the southern United States, the prevalence of cholelithiasis among end-stage kidney disease patients awaiting kidney transplants was 12%, with half of them being symptomatic.

Nephrogenic ascites are another GI disorder that affects dialysis patients; they are uncommon (probably $< 5\%$) and appear to be declining. Nephrogenic ascites is a clinical diagnosis defined as refractory ascites in patients with end-stage kidney disease where infection, portal hypertension, liver failure, and malignant processes are excluded. Most of these patients are undergoing HD. The exact cause of ascites formation is unclear, and patients frequently present with moderate to massive ascites and cachexia. The ascitic fluid has a high protein content, low serum-ascites albumin gradient, and low leukocyte count. Hypoalbuminemia may predispose uremic patients to ascites development. The diagnosis is made by ruling out other causes, and it has been suggested that the pathogenesis of the ascites is an alteration in peritoneal membrane permeability or impaired resorption due to peritoneal lymphatic channel obstruction. Daily HD should be the initial therapy and is successful in up to three-fourths of patients within 3 weeks. Alternative approaches include continuous ambulatory peritoneal dialysis, with renal transplantation being the most effective form of therapy, with the success rate approaching 100%.

Conclusions

Liver disease is currently a significant cause of morbidity and mortality among patients receiving long-term dialysis. Hepatitis B and C infections are important causes of dialysis-associated liver disease. DAA agents will change the natural history of chronic hepatitis C in these patients as their use continues to grow. Compliance with infection control procedures against blood-borne pathogens is recommended to control HCV and HBV infections within dialysis facilities; isolation of HBsAg-positive patients is also needed to limit HBV spread. GI disorders are frequently encountered among patients on chronic dialysis, even if the prevalence of *H. pylori* is not greater than that observed in patients with intact kidney function.

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Abnormalities of Thyroid Function in Chronic Dialysis Patients

CONNIE M. RHEE, MD, MSc

Introduction

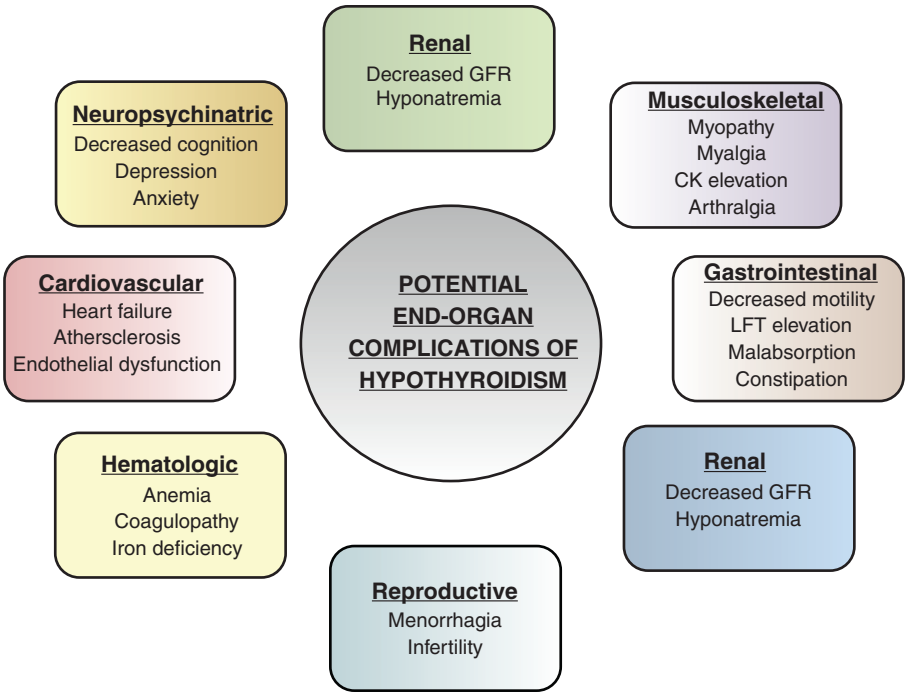
Chronic kidney disease (CKD) patients, including those receiving dialysis, have a substantially higher prevalence of hypothyroidism compared to their non-CKD counterparts (i.e., 25% vs. 5%, respectively). However, there is often underrecognition of this metabolic disorder in dialysis patients, given that hypothyroid-related symptoms (i.e., fatigue, cold intolerance, impaired cognition, and depression) may overlap with uremia and coexisting comorbidities. Hypothyroidism is typically ascertained by biochemical tests, which include an elevated serum thyrotropin (TSH) level (i.e., the most sensitive and specific single biochemical metric of thyroid status), which, in conjunction with a low or normal free thyroxine (FT4) level, indicates overt ("moderate-to-severe") hypothyroidism or subclinical ("mild") hypothyroidism, respectively. Dialysis patients also frequently demonstrate other thyroid function test derangements, such as low triiodothyronine (T3), low T4, and high reverse T3 (rT3) levels.

As thyroid hormone receptors are present in nearly all tissues, in the general population, hypothyroidism has been shown to have pervasive effects on multiple end-organs, particularly the cardiovascular system, if left untreated (Fig. 52.1). While hypothyroidism was previously thought to be a physiologic adaptation in patients with end-stage kidney disease (ESKD) who are prone to hypercatabolism, malnutrition, and dialytic protein and amino acid losses, growing evidence has shown that hypothyroidism is associated with adverse outcomes, including cardiovascular disease, worse patient-centered outcomes (i.e., impaired health-related quality of life [HRQOL]), and higher mortality risk. In this chapter, we review: (1) the epidemiology of hypothyroidism and other thyroid functional test alterations commonly observed in dialysis patients, (2) the mechanistic pathways linking thyroid and kidney disease, and (3) recent data on the prognostic implications and treatment of hypothyroidism in this population.

Epidemiology of Thyroid Dysfunction in Kidney Disease

Large population-based studies show that there is an incrementally higher prevalence of hypothyroidism with increasingly impaired kidney function (Table 52.1). Data from 14,623 adults in the Third National Health and Nutritional Examination Survey (NHANES III) have demonstrated that the prevalence of hypothyroidism (defined as TSH >4.5 mIU/L or treatment with exogenous thyroid hormone) was 5%, 11%, 20%, 23%, and 23% among those with estimated glomerular filtration rates (eGFRs) of >90, 60–89, 45–59, 30–44, and <30 mL/min/1.73m^2, respectively. Even after accounting for differences in age, sex, and race/ethnicity using multivariable logistic regression, there remained a twofold higher risk of hypothyroidism among participants with an eGFR <30 vs. those with an eGFR ≥90 mL/min/1.73m^2. This study also showed that over 50% of hypothyroid cases had subclinical disease (defined as TSH >4.5 mIU/L and total T4 ≥4.5 μg/dL). In a more recent study of 461,607 U.S. Veterans with stages 3–5 CKD, each 10 mL/min/1.73m^2 decrement in eGFR was associated with an 18% higher risk of hypothyroidism (defined as TSH >5 mIU/L and/or receipt of thyroid hormone replacement therapy), independent of age, sex, race/ethnicity, and comorbidities. In another recent analysis of a diverse community-based cohort of 378,101 patients from Kaiser Permanente Southern California, 30.4% of individuals had hypothyroidism, and in adjusted analyses, patients with hypothyroidism were more likely to have CKD vs. those with euthyroidism.

While studies examining thyroid status in ESKD have been conducted in comparatively smaller cohorts, a similarly high prevalence of hypothyroidism has been observed in hemodialysis and peritoneal dialysis patients (see Table 52.1). Varying prevalence estimates across these studies may be due to differences in the criteria used to define hypothyroidism, age distribution, and iodine intake of the study populations.



• **Fig. 52.1** End-organ complications of hypothyroidism. *CK*, Creatinine kinase; *GFR*, glomerular filtration rate; *LFT*, liver function test.

TABLE 52.1 Selected Studies of the Prevalence of Hypothyroidism and Thyrotropin Elevation in Dialysis Patients

Study (Year)	Cohort (N)	Definition of Thyroid Functional Disease	Prevalence
TSH Elevation			
Lin et al. (1998)	HD/PD (221)	TSH >3.1 mIU/L	14.9%
Kutlay et al. (2005)	HD (87)	TSH >5.5 mIU/L	23.1%
Rhee et al. (2013)	HD/PD (2715)	TSH >assay ULN	12.9%
Dreschler et al. (2014)	HD (1000)	TSH 4.5–15.0 mIU/L	1.8%
Rhee et al. (2015)	HD (8840)	TSH >5.0 mIU/L	21.8%
Rhee et al. (2016)	PD (1484)	TSH >5.0 mIU/L	18.0%
Rhee et al. (2017)	HD (541)	TSH >5.0 mIU/L	10.5%
Subclinical Hypothyroidism			
Shantha et al. (2011)	HD (137)	TSH 4.5–10 mIU/L + Normal FT4	24.8%
Ng et al. (2012)	PD (122)	TSH >4 mIU/L + Normal FT4	15.6%

Continued

TABLE 52.1 Selected Studies of the Prevalence of Hypothyroidism and Thyrotropin Elevation in Dialysis Patients—cont'd

Study (Year)	Cohort (N)	Definition of Thyroid Functional Disease	Prevalence
Meuwese et al. (2012)	HD (218)	Diagnostic criteria not available	1.8%
Rhee et al. (2013)	HD/PD (2715)	TSH: assay ULN to 10 mIU/L	8.9%
Dreschler et al. (2014)	HD (1000)	TSH 4.5–15.0 mIU/L + Normal FT3/FT4	1.6%
Rhee et al. (2015)	HD (8840)	TSH >5.0–10 mIU/L	12.9%
Rhee et al. (2016)	PD (1484)	TSH >5.0–10 mIU/L	11.7%
Overt Hypothyroidism			
Kaptein et al. (1988)	HD (306)	(1)TSH ≥20 mIU/L, OR (2) TSH 10–20 mIU/L + exaggerated TRH response + Low TT4 or FT4 index	2.6%
Lin et al. (1998)	HD/PD (221)	TSH ≥20 mIU/L + Low TT4 or FT4	5.4%
Kutlay et al. (2005)	HD (87)	TSH >5.5 mIU/L + Low FT4	3.4%
Meuwese et al. (2012)	HD (218)	Diagnostic criteria not available	5.0%
Rhee et al. (2013)	HD/PD (2715)	TSH >10 mIU/L	4.3%
Dreschler et al. (2014)	HD (1000)	TSH 4.5–15.0 mIU/L + Normal FT3/FT4	0.2%
Rhee et al. (2015)	HD (8840)	TSH >10 mIU/L	8.9%
Rhee et al. (2016)	PD (1484)	TSH >10 mIU/L	6.5%

HD, hemodialysis; *FT4*, free thyroxine; *FT3*, free triiodothyronine; *PD*, peritoneal dialysis; *TRH*, thyrotropin-releasing hormone; *TSH*, thyrotropin; *TT4*, total thyroxine; *ULN*, upper limit of normal.

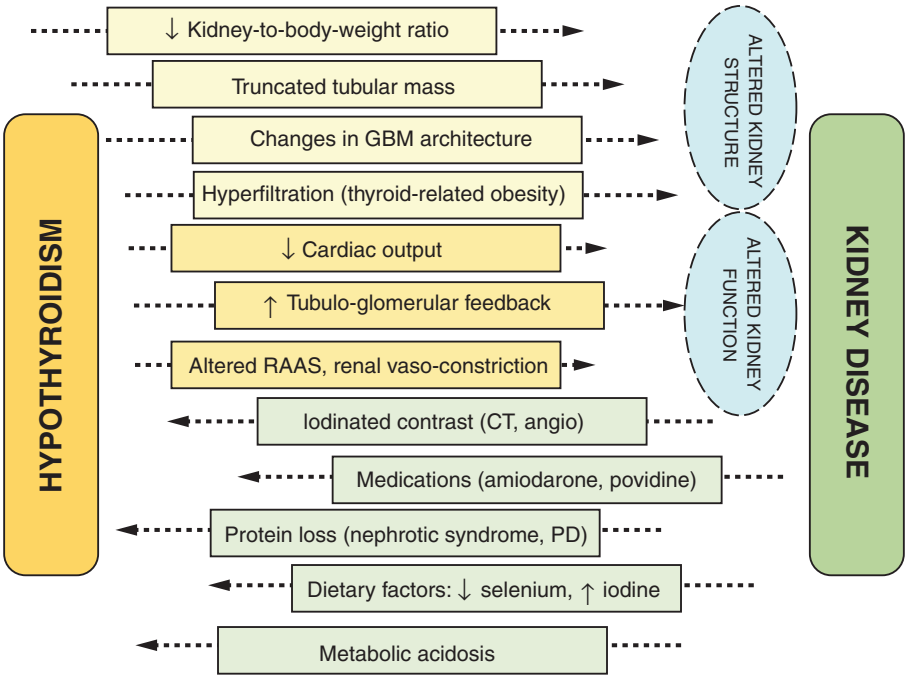
Factors Contributing to Thyroid Dysfunction in Kidney Disease

Normal Thyroid Hormone Physiology

The production of thyroid hormone is stimulated by TSH from the pituitary, which in turn is regulated by TSH-releasing hormone (TRH) from the hypothalamus. While T4 is solely produced by the thyroid gland, 80% of T3 is generated from the deiodination of T4-to-T3 by the type 1 and 2 5'-deiodinase enzymes (D1 and D2) in peripheral tissues. In humans, D2 is believed to be the principal enzyme responsible for peripheral T4-to-T3 production. Consequently, both TSH and TRH are regulated by feedback inhibition from circulating T4, which is converted to T3 in the pituitary and hypothalamus by D2.

Thyroid Functional Disease Leading to Kidney Disease

While the mechanistic link between thyroid and kidney disease has not been fully elucidated, growing data suggest



• **Fig. 52.2** Bidirectional relationship between hypothyroidism and kidney disease. *CT*, Computed tomography; *GBM*, glomerular basement membrane; *PD*, peritoneal dialysis; *RAAS*, renin–angiotensin–aldosterone.

the relationship is bidirectional (Fig. 52.2). With respect to thyroid dysfunction as a risk factor for CKD, experimental models have shown that hypothyroidism adversely affects *kidney size and structure* both in development and adulthood. For example, in neonatal rats, hypothyroidism has been shown to result in decreased kidney-size-to-body-weight-ratio, truncated tubular mass, and decreased glomerular basement membrane (GBM) volume. Hypothyroidism has also led to diminished compensatory hypertrophy following unilateral nephrectomy in animal models, and histologic data has demonstrated that hypothyroidism is associated with GBM architectural changes such as reduced GBM area, GBM thickening, mesangial matrix expansion, and glomerular capillary permeability.

Hypothyroidism may also lead to *decreased kidney function*, presumably due to reduced kidney blood flow from (1) decreased cardiac output resulting from systolic dysfunction, diastolic impairment, and decreased blood volume, (2) intrarenal hemodynamic derangements due to impaired vasodilator (e.g., nitric oxide, adrenomedullin) synthesis and activity, (3) decreased renin-angiotensin-aldosterone activity leading to impaired autoregulation of kidney perfusion, and (4) alterations in chloride channel expression with increased distal tubular chloride delivery, kidney afferent arteriole vasoconstriction, and lower glomerular filtration rate (GFR) (i.e., increased tubulo-glomerular feedback). For example, animal studies have shown that hypothyroidism leads to decreased single nephron GFR, kidney plasma flow, and glomerular transcapillary hydrostatic pressure. Human case series have also confirmed that severe hypothyroidism results in reversible plasma flow reductions, serum creatinine elevations, and decreased GFR as measured by indirect estimating equations and gold standard isotopic kidney scans, confirming that changes in creatinine levels were due to actual changes in GFR as opposed to underlying myopathy or alterations in creatinine metabolism.

In large population-based studies, while multiple cross-sectional analyses corroborate a link between milder forms of hypothyroidism and kidney dysfunction, longitudinal studies have been sparse, with mixed findings. In a longitudinal study of 104,633 patients with normal baseline kidney function who underwent annual to biennial TSH measurements, patients whose baseline TSH levels were in the highest quintile (TSH 2.85–5.00 mIU/L) had a 26% higher risk of incident CKD (defined as eGFR < 60 mL/min/1.73m^2) vs. those in the lowest TSH quintile (TSH 0.25–1.18 mIU/L). Similarly, in a study of 41,454 elder adults with normal baseline kidney function who underwent repeated TSH measurements over time, those with subclinical hypothyroidism (defined as TSH > 3–5 mIU/L) and overt hypothyroidism (defined as TSH > 10–99 mIU/L) were each at higher risk of developing subsequent CKD (defined as eGFR < 60 mL/min/1.73m^2 or abnormal proteinuria levels) compared to those who were euthyroid. Yet in studies of the Atherosclerosis Risk in Communities Study and Leiden-85 Plus (i.e., population-based study of 85-year old residents of Leiden, the Netherland) cohorts, whereas cross-sectional analyses showed that baseline hypothyroidism was associated with kidney dysfunction, longitudinal analyses of these cohorts did not confirm a relationship with incident CKD or eGFR decline. However, it bears mentioning that these two studies assessed TSH levels only at a single point in time (i.e., baseline TSH only), which may have led to thyroid status misclassification over time. It should also be noted that cystatin C should not be used as a metric

of kidney function in patients with thyroid functional disease, given that its production may be affected by thyroid hormone independent of GFR.

Limited observational data also suggest that thyroid hormone replacement is associated with reduced CKD progression in patients with subclinical hypothyroidism. In a study of 309 patients with stages 2–4 CKD and subclinical hypothyroidism, after a median follow-up of 35 months, patients who received thyroid hormone replacement therapy were less likely to experience a halving of eGFR or development of incident ESKD compared to those who were untreated. Given the potential role of thyroid dysfunction as a modifiable risk factor for kidney disease, further studies are needed to determine the longitudinal impact of thyroid status and its treatment upon incident CKD and CKD progression.

Kidney Disease Leading to Thyroid Functional Disease

Kidney disease may also lead to thyroid functional disease via several pathways (see Fig. 52.2). First, metabolic acidosis has been associated with lower T3, lower T4, and higher TSH levels in nondialysis patients. In one study of hemodialysis patients, correction of metabolic acidosis with sodium citrate normalized FT3 concentrations but had no impact on FT4 or TSH levels. In a secondary analysis of hemodialysis patients from the Frequent Hemodialysis Network (FHN) Trials, while significant correlations were observed between changes in serum bicarbonate and changes in FT3 and FT4 levels, these findings were no longer significant after adjusting for changes in normalized protein catabolic rate (nPCR) levels; notably, this study excluded patients with serum TSH levels >8 mIU/L and/or received thyroid hormone supplementation who were presumed to have treated or untreated hypothyroidism and did not take into consideration TSH levels in the analyses. Second, selenium deficiency is common in hemodialysis patients and may impair peripheral T4-to-T3 conversion, leading to lower T3 levels. Third, iodine retention from iodinated contrast-enhanced imaging studies, fistulograms, angiograms, povidone-iodine solutions used to sterilize peritoneal dialysis catheter tips, and dietary sources may lead to hypothyroidism via the Wolff-Chaikoff effect or hypothyroidism via the Jod-Basedow phenomenon. Fourth, testosterone deficiency is also common in dialysis patients, and animal studies have been associated with reduced peripheral deiodination of T4-to-T3. Fifth, as the vast majority of circulating T3 and T4 (>99%) are bound to carrier proteins such as thyroid-binding globulin, transthyretin, albumin, and lipoproteins, heavy urinary losses of these proteins in nephrotic syndrome may lead to thyroid hormone deficiency. Sixth, malnutrition, inflammation, and underlying comorbidities prevalent in dialysis patients may lead to nonthyroidal illness (i.e., thyroid function test alterations associated with underlying ill health in the absence of thyroid pathology) (Table 52.2). Lastly, various medications commonly prescribed in dialysis patients may lead to thyroid function test alterations (Table 52.3).

TABLE 52.2 Thyroid Function Tests in Nonthyroidal Illness

Severity of Illness	Thyroid Function Test		
	T3	T4	TSH*
Mild	↓	Normal	Normal
Moderate	↓↓	↓	Normal
Severe	↓↓	↓↓	↓

* TSH usually normal in nonthyroidal illness. In the recovery phase of severe illness, transient rise in T3, T4, and TSH may be seen.
TSH, Thyrotropin.

TABLE 52.3 Common Medications in Dialysis Patients That Alter Thyroid Function Test Results

Mechanism	Medications
↓ Thyroid hormone synthesis/secretion	Thionamides
	Lithium
	Iodine-containing agents/ medications
↓ Thyroxine absorption	Calcium carbonate
	Sevelamer
	Lanthanum carbonate
	Aluminum hydroxide
	Iron sulfate
	Proton pump inhibitors
	Cholestyramine
	Colestipol
↓ Thyrotropin	Dopamine
	Dobutamine
	Glucocorticoids
↑ Thyroid hormone synthesis/secretion	Amiodarone
	Iodine-containing agents/ medications
Impaired thyroxine-hormone binding	Furosemide
	Heparin
	Salicylates
	NSAIDs
Impaired T4-to-T3 conversion	Amiodarone
	Glucocorticoids
	Propranolol
	Nadolol
	Propylthiouracil

NSAIDs, Nonsteroidal anti-inflammatory drugs.

Effects of Dialysis on Thyroid Function Tests

Limited data suggest that dialysis therapy may contribute to alterations in thyroid hormone metabolism. Two case series of peritoneal dialysis patients demonstrated that 10%–30% of daily T4 production was lost in peritoneal dialysis effluent as a free and protein-bound hormone; however, some have posited that the predominant etiology of hypothyroidism in peritoneal dialysis patients is iodine excess from povidine-iodine cleaning agents as opposed to peritoneal effluent thyroid hormone losses. In hemodialysis patients, one study that measured thyroid function tests pre- and postdialysis showed that TSH levels remained stable, whereas T3 and T4 demonstrated a significant rise postdialysis; these changes were thought to be due to medication effects and extravascular shifts in thyroid hormone. Notably, in a secondary analysis of FHN trial participants among whom the prevalence of hypothyroidism was 11% (defined as receipt of thyroid hormone supplementation and/or having a TSH level ≥ 8 mIU/L), among patients in the in-center frequent hemodialysis and nocturnal home hemodialysis arms (i.e., receipt of hemodialysis six times per week), changes in TSH, FT3, and FT4 levels were not observed after a 12-month period. Yet, in another study of 22 incident hemodialysis patients, those who were treated with long nocturnal hemodialysis were less likely to have low FT3 levels vs. those treated with conventional hemodialysis.

Thyroid Function Test Alterations in Dialysis Patients

The kidney bears an important role in the metabolism, degradation, and excretion of thyroid hormone and its metabolites. Uremic toxins may also alter the hypothalamic-pituitary-thyroid axis pathway and the performance of thyroid hormone assays. As a result, various thyroid function test alterations may be observed in euthyroid dialysis patients (Table 52.4).

Low Triiodothyronine (Low Triiodothyronine Syndrome)

Low T3 levels are the most commonly observed thyroid function test alteration in kidney disease patients. In a cross-sectional cohort of 2284 nondialysis-dependent (NDD)-CKD patients with normal TSH levels, there was a graded association between the prevalence of low T3 with incrementally lower eGFRs: 8%, 11%, 21%, 61%, and 79% for eGFR levels ≥ 90, 60–<90, 30-<60, 15–<30, and <15 mL/min/1.73m^2, respectively. In dialysis patients, a similarly high prevalence of low T3 has been observed.

The peripheral deiodination of T4 to T3 is highly sensitive to illness states, and low T3 levels are the most common thyroid function test alteration observed in nonthyroidal illness (see Table 52.2). Multiple factors may lead to reduced

TABLE 52.4 Common Thyroid Functional Disease Alterations in Dialysis Patients

Thyroid Function Test	Alterations
Triiodothyronine (T3)	• Low T3 levels due to decreased peripheral T4-to-T3 conversion due to uremia, malnutrition, illness
	• Impaired binding of T3 to thyroid hormone nuclear receptors
	• Impaired T3-induced transcriptional activation
Reverse triiodothyronine (rT3)	• Normal rT3 levels
Total thyroxine (TT4)	• Decreased TT4 levels due to low protein states
Free thyroxine (FT4)	• Spurious FT4 levels due to impaired hormone-protein binding associated with uremia, nonthyroidal illness, low protein states, medications (indirect FT4 assay methods)
	• Impaired FT4 cellular uptake
Thyrotropin (TSH)	• Decreased clearance
	• Blunted response to TRH
	• Decreased pulsatility
	• Increased half-life
	• Impaired glycosylation
Anti-TPO antibody	• Limited data suggest that higher anti-TPO antibody levels correlate with higher TSH levels in dialysis patients.

TPO, Thyroid peroxidase; *TRH*, thyrotropin-releasing hormone.
Adapted from Rhee CM, Brent GA, Kovesdy CP, et al. Thyroid functional disease: an under-recognized cardiovascular risk factor in kidney disease patients. *Nephrol Dialysis Transplant* 2015;30(5):724-737.

conversion of T4 to T3 in nonthyroidal illness, which include malnutrition; cytokines, such as tumor necrosis factor, interferon-α, nuclear factor kappa B (NF-κβ), and interleukin-6 (IL-6); high endogenous serum cortisol levels and exogenous glucocorticoids; free nonesterified fatty acids; and certain medications (e.g., amiodarone). Indeed, cross-sectional data in hemodialysis and peritoneal dialysis patients have shown an inverse association between T3 and IL-6, IL-10, C-reactive protein (CRP), and albumin, suggesting that low T3 may be a marker of inflammation and malnutrition in these populations.

Reverse Triiodothyronine

While the D1 and D2 enzymes produce biologically active T3, in nonthyroidal illness, there is (1) increased conversion of T4 to rT3, a metabolically inactive form of thyroid hormone, and (2) reduced degradation of rT3 to inactive diiodothyronine via the type 3 5'-deiodinase (D3) enzyme, leading to higher rT3 levels. In the general population, rT3 levels are low in hypothyroidism. However, in dialysis patients, rT3 levels are typically normal; at this time, the clinical significance of rT3 in dialysis patients is not known.

Low Thyroxine

Low levels of total T4 (TT4) and FT4 are also commonly reported in patients on dialysis; however, it has been suggested that a proportion of these cases may be falsely low due to the impact of low protein states, uremia, nonthyroidal illness, and medication effects on thyroid function test accuracy. TT4 levels, which capture both free and protein-bound thyroid hormone, may be depressed in patients with low protein levels, given that the vast majority of T4 is protein bound. Furthermore, FT4 levels, which are intended to measure the biologically active form of T4, may be inaccurate in euthyroid dialysis patients due to uremia, nonthyroidal illness, and medication effects. In the clinical setting, indirect FT4 assays (e.g., FT4 analog assay or FT4 index) are widely used, which estimate the minute fraction of FT4 using TT4 levels and a binding protein estimate. While indirect FT4 assays are generally accurate, they are protein-hormone binding dependent. Thus, in conditions where serum protein levels are low (e.g., malnutrition) or circulating substances impair hormone-protein binding (e.g., uremia, nonthyroidal illness, heparin, furosemide), indirect FT4 assays are likely to result in spurious FT4 levels and disease misclassification. In contrast, direct FT4 assays more accurately discern FT4 by (1) physically separating free from protein-bound hormone using equilibrium dialysis or ultrafiltration, followed by (2) FT4 quantification using radioimmunoassay or tandem mass spectrometry. Compared to indirect FT4, direct FT4 levels have been shown to be more strongly correlated with TSH (suggesting more accurate thyroid function assessment) and to be weakly correlated with albumin (suggesting less confounding by protein-energy wasting) in populations with normal and altered hormone-protein binding (e.g., pregnancy). Direct FT4 assays are currently not available outside of reference laboratories, and their accuracy in dialysis patients requires further study.

Elevated Thyrotropin

TSH is the most sensitive and specific single biochemical metric of thyroid function in the general population, and it is used to screen, diagnose, and monitor treatment in primary hypothyroidism. TSH levels typically remain normal in nonthyroidal illness but can be depressed in severe, critically ill states or transiently elevated in the recovery phase of illness.

However, it should be noted that some TSH alterations may be observed in dialysis patients, including reduced clearance, blunted response to TRH, decreased pulsatility, impaired glycosylation and bioactivity, and increased half-life. In one study of 38 dialysis patients, TSH and FT4 were found to be more reliable indicators of thyroid function vs. T3 using various metabolic tests as a proxy for thyroid functional status.

One caveat of the aforementioned tests is that serum levels of thyroid function tests may not per se reflect tissue levels. However, a biochemical test or physiologic measure that is sufficiently sensitive and specific in measuring thyroid function at the tissue level has not yet been identified. Further efforts are needed to define the optimal approach to thyroid function testing in dialysis patients.

Anti–Thyroid Peroxidase Antibodies

Thyroid peroxidase (TPO) is a membrane-associated glycoprotein that catalyzes the iodination of tyrosine residues and their coupling to form the thyroid hormones T3 and T4, in a process known as organification. Anti-TPO antibodies may be found in the presence and absence of autoimmune thyroid disease. In studies of the non-CKD population, the prevalence of anti-TPO antibody elevation in subclinical hypothyroidism has varied according to age, sex, and race/ethnicity. On average, 60%–80% of patients with subclinical hypothyroidism and/or elevated TSH have elevated anti-TPO antibody levels. In studies of dialysis-dependent CKD patients, limited data have shown that a smaller proportion (i.e., 20%–30%) of those with elevated TSH levels have elevated anti-TPO antibody levels compared with the non-CKD population. However, in one prospective study of 996 hemodialysis patients who underwent concurrent anti-TPO antibody and TSH measurements, those with elevated anti-TPO antibody levels had higher TSH levels vs. those with normal anti-TPO antibody levels. These findings suggest that the high prevalence of hypothyroidism in dialysis patients may only partially be explained by autoimmune causes, although further study of the interplay between circulating anti-TPO antibodies and TSH in the CKD population is needed.

Thyroid Functional Disease and Outcomes in Dialysis Patients

An increasing body of evidence shows that hypothyroidism and other thyroid function test derangements are associated with a higher risk of death, cardiovascular disease, and worse patient-centered outcomes in CKD patients, including those receiving dialysis.

Survival

Serum Thyrotropin Levels and Survival

Multiple studies have shown that hypothyroidism, defined by elevated TSH levels, is associated with higher mortality risk across various dialysis-dependent and NDD-CKD cohorts (Table 52.5). In one of the first of these studies, among 2715 hemodialysis and peritoneal dialysis patients from two academic medical centers who underwent baseline TSH measurement, those who were hypothyroid had a 27% higher all-cause mortality risk compared to those who were euthyroid. Yet in a subsequent study of 1000 diabetic hemodialysis patients from the Die Deutsche Diabetes Dialyse Studie (4D Study), subclinical hypothyroidism examined separately or in conjunction with overt hypothyroidism was not associated with sudden cardiac death, cardiovascular events, or all-cause mortality; however, the low prevalence of hypothyroidism (1.8%) in this cohort may have resulted in limited power to detect significant associations. Notably, the interpretation of findings from these studies is limited by their assessment of thyroid status at a single point in time only and mixed examination of the incident and prevalent dialysis patients who have differential survival characteristics.

To address these knowledge gaps, in a subsequent study that examined 8840 incident hemodialysis patients from a large national dialysis organization who underwent repeated TSH measurements over time, baseline and time-varying hypothyroidism were each associated with a 47% and 62% higher all-cause mortality risk, respectively. When examined in finer gradations, higher TSH levels even in the normal range (TSH >3–5 mIU/L) were associated with a 30% and 42% higher mortality risk in baseline and time-varying analyses, respectively, compared to levels in the low-normal range (TSH 0.5–3 mIU/L). Four subsequent studies that examined repeated measures of TSH over time in other dialysis-dependent CKD and NDD-CKD cohorts have found that hypothyroidism and/or high-normal TSH levels are associated with higher death risk. In a study of 1474 peritoneal dialysis patients from a large dialysis organization, both time-varying hypothyroidism and hyperthyroidism were each associated with higher mortality. Among a prospective cohort of 541 hemodialysis patients from the Hypothyroidism, Cardiovascular Disease, and Survival in Kidney Disease (HyCARDS) study who underwent protocolized TSH measurements every 6 months, time-varying TSH levels in the highest tertile (TSH >2.11

TABLE 52.5 Selected Studies of Thyroid Status Defined by Serum Thyrotropin (TSH) Levels and Mortality in Dialysis-Dependent and Nondialysis-Dependent Chronic Kidney Disease Patients

Study (Year)	Cohort (N)	TSH Threshold (mIU/L)	Outcome
Mortality			
Rhee et al. (2013)	HD + PD (2715)	TSH ≥3.0	↑ All-cause mortality
Dreschler et al. (2014)	HD (1000)	TSH ≥4.1	No association between TSH with death; however, ↓ FT3 associated with ↑ all-cause mortality during first year of observation
Rhee et al. (2015)	HD (8840)	TSH ≥3.0	↑ All-cause mortality
Rhee et al. (2016)	PD (1484)	TSH >5.0	↑ All-cause mortality
Rhee et al. (2017)	HD (541)	TSH >2.1	↑ All-cause mortality
Rhee et al. (2018)	Stage 3 NDD-CKD (232,524)	TSH >3.0	↑ All-cause mortality
You et al. (2018)	Advanced NDD-CKD transitioning to ESKD (15,335)	TSH >5.0	↑ All-cause mortality

CKD, Chronic kidney disease; *ESKD*, end-stage kidney disease; *FT3*, free triiodothyronine; *HD*, hemodialysis; *NDD*, nondialysis-dependent; *PD*, peritoneal dialysis; *TSH*, thyrotropin.

mIU/L) were associated with higher mortality risk. In a study of 227,422 U.S. Veterans with stage 3 CKD from the national Veterans Affairs (VA) database, both high-normal TSH levels and hypothyroidism were each associated with higher death risk in baseline and time-varying analyses. Finally, in a study of 15,335 US Veterans with advanced CKD transitioning to dialysis, hypothyroidism defined by time-averaged TSH levels in the pre-ESKD period was associated with higher post-ESKD mortality risk.

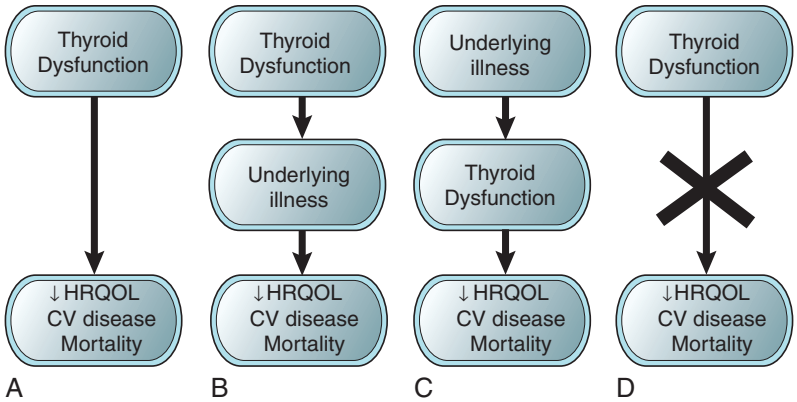
Notably, some data have shown differential associations between thyroid status with mortality risk according to markers of nutritional status. In the abovementioned study of incident hemodialysis patients from a large dialysis organization, associations of baseline thyroid status with mortality across body mass index (BMI) subgroups showed that these relationships were attenuated to the null in those with BMI ≤ 20 kg/m^2, while there was an incrementally stronger hypothyroidism–mortality association across higher BMI categories in time-varying analyses. On the basis of these data, it has been hypothesized that hypothyroidism's adverse effects may be nullified in malnourished dialysis patients in whom thyroid hormone deficiency is a physiologic response to reduce catabolism. Given that the observational design of these studies does not establish causality, further study is needed to determine hypothyroidism's role as a pathologic abnormality vs. marker of underlying illness vs. physiologic adaptation in select dialysis populations (Fig. 52.3).

Cardiovascular Disease

Given that cardiovascular disease is the leading cause of mortality in dialysis patients (i.e., 40% of all deaths), it has been hypothesized that hypothyroidism may be a risk factor for cardiovascular morbidity and mortality in this population. Indeed, the cardiovascular system is a major target of thyroid hormone action, and thyroid hormone has both genomic and nongenomic effects on a number of cardiac structural and regulatory proteins, membrane ion channels, and cell surface receptors. As a result, thyroid hormone deficiency has been associated with a diverse range of cardiovascular complications in the general population, including impaired systolic and diastolic function, endothelial dysfunction, dyslipidemia, accelerated atherosclerosis, vascular calcification, and conduction abnormalities leading to malignant arrhythmias (Table 52.6).

Serum Thyrotropin Levels and Cardiovascular Disease

Growing data show that hypothyroidism ascertained by serum TSH levels is associated with adverse cardiovascular surrogates in the dialysis population (Table 52.7). In a cross-sectional study of 51 peritoneal dialysis patients, patients with subclinical hypothyroidism had worse systolic function (i.e., lower left ventricular ejection fraction) compared to those who were euthyroid. In a subsequent secondary analysis of 99 hemodialysis patients from the Anti-Inflammatory and Anti-Oxidative Nutrition in Hypoalbuminemic Dialysis Patients (AIONID) trial, patients with TSH levels in the highest three quartiles had worse endothelial function as measured by novel digital thermal monitoring tests as a reactive hyperemia method vs. those in the lowest quartile. Given that thyroid hormone deficiency may lead to accelerated atherosclerosis (i.e., due to endothelial dysfunction and dyslipidemia) and vascular calcification (i.e., due to decreased production of vascular calcification inhibitors such as matrix gla protein and klotho), there has been growing interest in hypothyroidism as a risk factor for coronary artery calcification (CAC) in kidney disease. In secondary analyses of 104 patients from the AIONID trial, incrementally higher TSH levels were associated with a higher CAC burden. However, in another study of 94 ESKD patients eligible for living donor transplantation, lower TSH, FT3, and FT4 levels were associated with higher CAC scores. Yet in another study of 84 peritoneal patients, low FT3 levels were associated with higher CAC scores measured by cardiac CT scan; although TSH levels were also measured, associations with CAC were not reported.



• **Fig. 52.3** Potential pathways linking thyroid functional disease and adverse outcomes in dialysis patients. (A) Thyroid dysfunction is causally associated with adverse outcomes. (B) Thyroid dysfunction is a marker of underlying illness, which in and of itself is associated with adverse outcomes. (C) Thyroid dysfunction mediates the association between underlying illness and adverse outcomes. (D) Thyroid dysfunction is not associated with adverse outcomes in certain populations (i.e., dialysis patients with protein-energy wasting). *CV*, Cardiovascular; *HRQOL*, health-related quality of life.

TABLE 52.6 Cardiovascular Complications of Hypothyroidism

Cardiovascular System	Sequelae of Hypothyroidism	Pathogenesis
Cardiac function	• ↓ Systolic and diastolic function • ↓ Cardiac output	• Altered transcription of myocyte contractility and relaxation genes • Alteration of cardiac ion channels • ↓ Peripheral oxygen consumption and requirements • ↓ Erythropoietin and erythrocytosis ➔ ↓ blood volume
Endothelial function	• Arterial stiffness • Impaired vasoreactivity • ↑ Systemic vascular resistance • Diastolic hypertension	• ↓ Vasodilator synthesis and activity • ↓ Tissue thermogenesis and metabolic activity
Metabolic status	• ↑ Total cholesterol • ↑ LDL • ↑ Triglycerides	• ↓ Catabolism of cholesterol into bile by cholesterol 7-alpha-hydroxylase enzyme • ↓ Hepatic LDL receptor density and activity ➔ ↓ fractional clearance of LDL
Vascular disease	• Atherosclerosis • Vascular calcification	• Dyslipidema • Hyperhomocysteinemia • Hypertension • ↓ Vascular calcification inhibitors: matrix Gla and klotho
Cardiac conduction	• Ventricular arrhythmia	• Changes in cardiac ion channel expression ➔ prolongation of QT interval

LDL, Low-density lipoprotein.

TABLE 52.7 Selected Studies of the Association of Thyroid Status with Cardiovascular Disease and Patient-Centered Outcomes in Dialysis Patients

Study (Year)	Cohort (N)	Thyroid Metric	Outcome
Cardiovascular Disease			
Jaroszynski et al. (2005)	HD (52)	↓ FT3	↓ Ventricular depolarization
Zoccali et al. (2006)	HD + PD (234)	↓ FT3	↓ LV systolic function ↑ LV mass
Kang et al. (2008)	PD (51)	TSH >5.0 mIU/L + Normal FT4	↓ LV ejection fraction
Tatar et al. (2011)	HD (137)	↓ FT3	↑ Atherosclerosis ↑ Arterial stiffness
Tatar et al. (2012)	PD (57)	↓ FT3	↑ Arterial stiffness
Saito et al. (2012)	HD (52)	↓ FT3	↑ Interstitial edema

Continued

TABLE 52.7 Selected Studies of the Association of Thyroid Status with Cardiovascular Disease and Patient-Centered Outcomes in Dialysis Patients—cont'd

Study (Year)	Cohort (N)	Thyroid Metric	Outcome
Meuwese et al. (2013)	PD (84)	↓ FT3	↑ Coronary artery calcification
Meuwese et al. (2015)	ESKD (97)	↓ FT3, FT4, TSH	↑ Coronary artery calcification
Rhee et al. (2018)	HD (104)	TSH >3.0 mIU/L	↑ Coronary artery calcification
You et al. (2018)	HD (99)	TSH >1.2 mIU/L	↓ Endothelial function
Musavi-Mehdiabadi et al. (2020)	PD (71)	↓ FT3	↑ LV mass index
Patient-Centered Outcomes			
Rhee et al. (2017)	HD (450)	TSH >2.1 mIU/L	↓ Health-related quality of life

ESKD, End-stage kidney disease; *FT3*, free triiodothyronine; *TSH*, thyrotropin; *FT4*, free thyroxine; *HD*, hemodialysis; *LV*, left ventricular; *PD*, peritoneal dialysis.

Low Triiodothyronine Levels and Cardiovascular Disease

As cardiac myocytes are unable to locally generate T3 from its T4 prohormone, there has been particular interest in T3 as the biologically relevant thyroid hormone metric for cardiovascular endpoints. In addition to the aforementioned data examining CAC endpoints, other studies have also shown that low circulating T3 levels are associated with adverse cardiovascular sequelae, including decreased systolic function, structural heart disease, arterial stiffness, and atherosclerosis in the dialysis population (see Table 52.7). However, given that T3 alterations are frequently seen with illness states, malnutrition, and inflammation, it remains unclear whether this observed T3–cardiovascular disease associations are confounded by nonthyroidal illness.

Patient-Centered Outcomes

As another potential pathway towards death, one study has examined the relationship between thyroid status and HRQOL in ESKD (see Table 52.7). In a prospective cohort of 450 hemodialysis patients with serial protocolized TSH and HRQOL Short Form 36 assessments, higher TSH levels were associated with impaired HRQOL scores. The Short Form 36 subscales most impaired in the setting of thyroid dysfunction were those related to physical health (i.e., energy/fatigue, physical function, role limitations due to physical health, pain). Hence, future studies are needed to determine the impact of thyroid status on physical health/function in dialysis patients and whether thyroid hormone supplementation improves the HRQOL and physical well-being of dialysis patients with thyroid dysfunction.

Treatment Considerations

The U.S. Renal Data System Annual Data Report has shown that exogenous thyroid replacement therapy in the form of levothyroxine is one of the most commonly prescribed medications among NDD-CKD and dialysis-dependent CKD Medicare Part D recipients. In the general population, several small clinical trials have shown that thyroid hormone supplementation in patients with subclinical hypothyroidism reverses diastolic dysfunction, dyslipidemia, endothelial dysfunction, and atherosclerosis over a relatively short time period (i.e., 3 to 6 months), although long-term safety and effectiveness studies in large population-based cohorts remain sparse. However, in one study of 4735 patients from the United Kingdom General Practitioner Research Database, levothyroxine treatment for subclinical hypothyroidism was associated with a 39% lower risk of fatal and nonfatal ischemic heart disease events in younger individuals (i.e., age 40 to 70 years), but no difference in outcomes among older patients (i.e., age >70 years). To date, there have been a sparse number of studies that have examined the impact of thyroid hormone supplementation in dialysis-dependent CKD and NDD-CKD patients, which are described below.

Exogenous Triiodothyronine Replacement

Previous data have shown that among hemodialysis patients with low T3 levels, exogenous T3 administered at higher than physiologic doses resulted in increased markers of protein degradation, raising concern that thyroid hormone replacement may exacerbate protein-energy wasting, a potent predictor of death in this population. In the general population, exogenous thyroid hormone treatment of hypothyroidism with T3 alone or in combination with T4 is typically not advised given wide fluctuations in serum T3 levels that may occur due to its rapid gastrointestinal absorption and short half-life (1 day).

Exogenous Thyroxine Replacement

In one study of 2715 hemodialysis patients examining T4 treatment status and thyroid function at a single point in time, compared to those with normal TSH levels and no treatment (i.e., presumed to be spontaneously euthyroid), those with normal TSH levels on treatment (i.e., presumed to be hypothyroid treated to target) had similar mortality risk, whereas those with high TSH not on treatment (i.e., uncontrolled or untreated hypothyroidism) had higher mortality risk. More recently, in a large retrospective analysis of 227,422 U.S. Veterans with stage 3 CKD from the national VA database, patients who were hypothyroid treated-to-TSH reference ranges with thyroid hormone replacement had similar to better survival vs. spontaneously euthyroid patients, whereas untreated and undertreated hypothyroidism were associated with higher mortality risk.

In light of limited evidence, using a conservative therapeutic approach in dialysis patients akin to that of non-CKD populations who are older or have underlying cardiovascular disease may be preferred. While the typical starting dose in healthy young adults is 1.6 μg/kg/day, a lower dose of 25 to 50 μg/day may be considered in dialysis patients. Given the long 1-week half-life of levothyroxine, a steady state is typically achieved 6 weeks after initiation of therapy or dose adjustment. At that time, clinical symptoms should be re-evaluated, and a repeat TSH level should be measured.

It should be noted that levothyroxine has a narrow toxic-to-therapeutic window, and it is possible that overreplacement or unwarranted treatment may lead to angina, myocardial infarction, atrial fibrillation, increased protein catabolism, and accelerated bone loss. There are presently clinical trials (i.e., THYROID-HD Trial) investigating the effects of thyroid hormone replacement in dialysis patients with high-normal and hypothyroid-range TSH levels on patient-centered and cardiovascular outcomes, which may shed greater light on the causal implications of hypothyroidism in dialysis patients. Furthermore, given their high prevalence of hypothyroidism, frequent use of levothyroxine, and high underlying cardiovascular risk, rigorous longitudinal studies are needed to determine the real-world safety and effectiveness of exogenous thyroid hormone treatment in the CKD population.

Suggested Reading

Barr ML, Chiu HK, Li N, et al. Thyroid dysfunction in children exposed to iodinated contrast media. *J Clin Endocrinol Metab.* 2016;101(6):2366–2370.

This is a case-control study showing that iodinated contrast media exposure was associated with a higher risk of incident hypothyroidism.

Chuang MH, Liao KM, Hung YM, Wang PY, Chou YC, Chou P. Abnormal thyroid-stimulating hormone and chronic kidney disease in elderly adults in Taipei City. *J Am Geriatr Soc.* 2016;64(6):1267–1273.

This is a large cohort study showing that hypothyroidism is associated with a higher risk of developing incident CKD in elderly patients without underlying kidney dysfunction at baseline.

Danzi S, Klein I. Thyroid disease and the cardiovascular system. *Endocrinol Metab Clin N Am.* 2014;43(2):517–528.

This article reviews various cardiovascular sequelae of thyroid functional disease.

Gavin LA, Eitan NF, Cavalieri RR, et al. Hypothyroidism induced by continuous ambulatory peritoneal dialysis. *West J Med.* 1983;138(4):562–565.

This is a case series describing the development of hypothyroidism among two peritoneal dialysis patients likely due to iodine exposure and retention.

Huang CW, Li BH, Reynolds K, Jacobsen SJ, Rhee CM, Sim JJ. Association between hypothyroidism and chronic kidney disease observed among an adult population 55 years and older. *Medicine (Baltimore).* 2020;99(17), e19569.

This is a study showing the relationship between hypothyroidism and CKD from a large, diverse community-based cohort from an integrated healthcare system.

Iglesias P, Diez JJ. Thyroid dysfunction and kidney disease. *Eur J Endocrinol.* 2009;160(4):503–515.

This article discusses the various mechanisms by which thyroid functional disease alters kidney function.

Inoue K, Ritz B, Brent GA, Ebrahimi R, Rhee CM, Leung AM. Association of subclinical hypothyroidism and cardiovascular disease with mortality. *JAMA Netw Open.* 2020;3(2), e1920745.

This study shows that cardiovascular disease mediated the associations of subclinical hypothyroidism and high-normal TSH concentrations with all-cause mortality in a large U.S. general population cohort.

Jonklaas J. Treatment of hypothyroidism. In: Braverman LE, Cooper DS, eds. *Werner and Ingbar's the Thyroid.* 10th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2013:611–628.

This book chapter discusses the management of hypothyroidism in the general population.

Jonklaas J, Kahric-Janicic N, Soldin OP, et al. Correlations of free thyroid hormones measured by tandem mass spectrometry and immunoassay with thyroid-stimulating hormone across 4 patient populations. *Clin Chem.* 2009;55(7):1380–1388.

This study compares the characteristics of indirect vs. direct FT4 assays, two different methods used to measure circulating free T4 levels, across populations with normal and abnormal hormone-protein binding states.

Kang EW, Nam JY, Yoo TH, et al. Clinical implications of subclinical hypothyroidism in continuous ambulatory peritoneal dialysis patients. *Am J Nephrol.* 2008;28(6):908–913.

This article is a study demonstrating the association between subclinical hypothyroidism and impaired left ventricular function.

Kaptein EM. Thyroid hormone metabolism and thyroid diseases in chronic kidney failure. *Endocr Rev.* 1996;17(1):45–63.

This article is a comprehensive review of various thyroid disorders and thyroid hormone test alterations observed in kidney disease.

Kaptein EM, Quion-Verde H, Chooljian CJ, et al. The thyroid in end-stage kidney disease. *Medicine.* 1988;67(3):187–197.

This article describes the frequency of goiter, primary hypothyroidism, and thyroid function test abnormalities in end-stage kidney disease patients.

Karanikas G, Schutz M, Szabo M, et al. Isotopic kidney function studies in severe hypothyroidism and after thyroid hormone replacement therapy. *Am J Nephrol.* 2004;24(1):41–45.

This is a case series describing patients who had reversible kidney dysfunction ascertained by isotopic kidney scans in the context of severe hypothyroidism.

Kerr DJ, Singh VK, Tsakiris D, et al. Serum and peritoneal dialysate thyroid hormone levels in patients on continuous ambulatory peritoneal dialysis. *Nephron.* 1986;43(3):164–168.

This article reports the proportion of T4 lost in peritoneal dialysate effluent among a case series of peritoneal dialysis patients.

Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. *N Engl J Med.* 2001;344(7):501–509.

This is a comprehensive review of the association between thyroid functional disease and cardiovascular disease.

Kreisman SH, Hennessey JV. Consistent reversible elevations of serum creatinine levels in severe hypothyroidism. *Arch Intern Med.* 1999;159(1):79–82.

This is a case series describing kidney dysfunction defined by serum creatinine levels among patients with severe hypothyroidism.

Kutlay S, Atli T, Koseogullari O, et al. Thyroid disorders in hemodialysis patients in an iodine-deficient community. *Artif Organs.* 2005;29(4):329–332.

This article reports the prevalence of thyroid functional disease in hemodialysis patients.

Ladenson PW. Diagnosis of hypothyroidism. In: Braverman LE, Cooper DS, eds. *Werner and Ingbar's the Thyroid.* 10th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2013:606–611.

This book chapter discusses the approach to diagnosing hypothyroidism, including biochemical testing, in the general population.

Lee SY, Rhee CM, Leung AM, Braverman LE, Brent GA, Pearce EN. A review: radiographic iodinated contrast media-induced thyroid dysfunction. *J Clin Endocrinol Metab.* 2015;100(2):376–383.

This is a review of iodinated contrast media exposure as a risk for developing thyroid disease.

Lim VS. Thyroid function in patients with chronic kidney failure. *Am J Kidney Dis.* 2001;38(4 suppl 1):S80–S84.

This article discusses the hypothesis that thyroid hormone deficiency is a physiologic adaptation in dialysis patients and reports data on hemodialysis patients who developed increased protein degradation after treatment with exogenous thyroid hormone.

Lin CC, Chen TW, Ng YY, et al. Thyroid dysfunction and nodular goiter in hemodialysis and peritoneal dialysis patients. *Perit Dial Int.* 1998;18(5):516–521.

This article describes the prevalence of TSH elevations and goiter in hemodialysis and peritoneal dialysis patients.

Lin YC, Chen TW, Yang WC, et al. Abnormal thyroid function predicts mortality in patients receiving long-term peritoneal dialysis: a case-controlled longitudinal study. *J Chin Med Assoc.* 2012;75(2):54–59.

This study describes the association between various thyroid function abnormalities and mortality in peritoneal dialysis patients.

Lo JC, Chertow GM, Go AS, et al. Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. *Kidney Int.* 2005;67(3):1047–1052.

This is one of the early studies demonstrating a graded association between hypothyroidism and incrementally impaired kidney function.

Lo JC, Beck GJ, Kaysen GA, et al. Thyroid function in end stage kidney disease and effects of frequent hemodialysis. *Hemodial Int.* 2017;21(4):534–541.

This is a secondary analysis of the FHN Trial examining the impact of frequent hemodialysis upon changes in thyroid function tests over time.

Mannemuddhu SS, Morgans HA, Pekkucuksen NT, Warady BA, Shoemaker LR. Hypothyroidism due to iodine overload in children receiving peritoneal dialysis: a report of 4 cases. *Am J Kidney Dis.* 2020;S0272-6386(20):30664–30668.

This is a case series of pediatric peritoneal dialysis patients who developed hypothyroidism after povidine iodine exposure.

Mariani LH, Berns JS. The kidney manifestations of thyroid disease. *J Am Soc Nephrol.* 2012;23(1):22–26.

This is a review describing the impact of thyroid function on kidney development, structure, hemodynamics, and function.

Musavi Mehdiabadi F, Rashidinejad A, Mahdavi A, Dehesh T. Relationship between thyroid hormones and left ventricular mass in peritoneal dialysis patients. *Iran J Kidney Dis.* 2020;14(5):380–388.

This is a study showing that low FT3 levels are associated with higher left ventricular mass index in peritoneal dialysis patients.

Meuwese CL, Carrero JJ, Cabezas-Rodriguez I, et al. Nonthyroidal illness: a risk factor for coronary calcification and arterial stiffness in patients undergoing peritoneal dialysis? *J Intern Med.* 2013;274(6):584–593.

This is an article reporting the association between low T3 levels and vascular calcification in peritoneal dialysis patients.

Meuwese CL, Gussekloo J, de Craen AJ, Dekker FW, den Elzen WP. Thyroid status and kidney function in older persons in the general population. *J Clin Endocrinol Metab.* 2014;99(8):2689–2696.

This study examined the relationship between thyroid status and kidney dysfunction in cross-sectional and longitudinal analyses.

Meuwese CL, van Diepen M, Cappola AR, et al. Low thyroid function is not associated with an accelerated deterioration in kidney function. *Nephrol Dial Transplant.* 2019;34(4):650–659.

This a pooled analysis of studies examining the relationship between thyroid status and kidney dysfunction.

Molfino A, Beck GJ, Li M, Lo JC, Kaysen GA, Investigators FHN. Association between change in serum bicarbonate and change in thyroid hormone levels in patients receiving conventional or more frequent maintenance haemodialysis. *Nephrology (Carlton).* 2019;24(1):81–87.

This is a secondary analysis of the FHN Trial examining whether changes in bicarbonate were associated with changes in thyroid function in patients with end-stage kidney disease receiving conventional or more frequent hemodialysis.

Netti GS, Rotondi M, Di Lorenzo A, et al. Nocturnal haemodialysis is associated with a reduced occurrence of low triiodothyronine serum levels in haemodialysed patients. *Clin Kidney J.* 2020;13(3):450–460.

This is a study showing that patients treated with long nocturnal hemodialysis are less likely to have low FT3 levels than those treated with conventional hemodialysis.

Ng YY, Wu SC, Da Lin H, et al. Prevalence of clinical and subclinical thyroid disease in a peritoneal dialysis population. *Perit Dial Int.* 2012;32(1):86–93.

This study examines the prevalence of thyroid functional disease in peritoneal dialysis patients.

Razvi S, Weaver JU, Butler TJ, et al. Levothyroxine treatment of subclinical hypothyroidism, fatal and nonfatal cardiovascular events, and mortality. *Arch Intern Med.* 2012;172(10):811–817.

This is a rigorous study reporting the association between correction of subclinical hypothyroidism with exogenous thyroid hormone and cardiovascular events in the general population.

Rhee CM, Bhan I, Alexander EK, Brunelli SM. Association between iodinated contrast media exposure and incident hyperthyroidism and hypothyroidism. *Arch Intern Med.* 2012;172(2):153–159.

This is the first case-control study to show that exposure to iodinated contrast media is associated with higher risk of incident hyperthyroidism and incident hypothyroidism.

Rhee CM, Alexander EK, Bhan I, et al. Hypothyroidism and mortality among dialysis patients. *Clin J Am Soc Nephrol.* 2013;8(4):593–601.

This is the first study reporting an association between hypothyroidism defined by TSH level and mortality in dialysis patients.

Rhee CM, Brent GA, Kovesdy CP, et al. Thyroid functional disease: an under-recognized cardiovascular risk factor in kidney disease patients. *Nephrol Dial Transplant.* 2015;30(5):724–737.

This is a review paper describing traditional and emerging pathways by which thyroid functional disease may impact cardiovascular health and survival in kidney disease patients.

Rhee CM, Curhan GC, Alexander EK, et al. Subclinical hypothyroidism and survival: the effects of heart failure and race. *J Clin Endocrinol Metab.* 2013;98(6):2326–2336.

This is a study showing the association between subclinical hypothyroidism and hypothyroidism overall with mortality is modified by underlying heart failure and race.

Rhee CM, Kalantar-Zadeh K, Streja E, et al. The relationship between thyroid function and estimated glomerular filtration rate in patients with chronic kidney disease. *Nephrol Dial Transplant.* 2015;30(2):282–287.

This is a large study of US veterans with chronic kidney disease reporting an association between kidney dysfunction and risk of hypothyroidism.

Rhee CM, Kim S, Gillen DL, et al. Association of thyroid functional disease with mortality in a national cohort of incident hemodialysis patients. *J Clin Endocrinol Metab.* 2015;100(4):1386–1395.

This is the largest study to date examining the association between hypothyroidism defined by TSH level and mortality in hemodialysis patients.

Rhee CM. Low-T3 syndrome in peritoneal dialysis: metabolic adaptation, marker of illness, or mortality mediator? *Clin J Am Soc Nephrol.* 2015;10(6):917–919.

This is an editorial discussing low FT3 as a potential marker of nonthyroidal illness in CKD.

Rhee CM, Kalantar-Zadeh K, Ravel V, et al. Thyroid status and death risk in US veterans with chronic kidney disease. *Mayo Clin Proc.* 2018;93(5):573–585.

This is a large-population based study examining the impact of thyroid dysfunction and its treatment upon survival in US Veterans with CKD.

Rhee CM, Ravel VA, Streja E, et al. Thyroid functional disease and mortality in a national peritoneal dialysis cohort. *J Clin Endocrinol Metab.* 2016;101(11):4054–4061.

This is a study examining the association of thyroid status with survival in peritoneal dialysis patients.

Rhee CM, You AS, Nguyen DV, et al. Thyroid status and mortality in a prospective hemodialysis cohort. *J Clin Endocrinol Metab.* 2017;102(5):1568–1577.

This is a study examining the association of thyroid status with survival in hemodialysis patients.

Rhee CM, Chen Y, You AS, et al. Thyroid status, quality of life, and mental health in patients on hemodialysis. *Clin J Am Soc Nephrol.* 2017;12(8):1274–1283.

This is a study examining the impact of thyroid status on self-reported HRQOL.

Ro K, Yuen AD, Du L, et al. Impact of hypothyroidism and heart failure on hospitalization risk. *Thyroid.* 2018;28(9):1094–1100.

This is a study examining the association of hypothyroidism and risk of hospitalization according to underlying cardiac status.

Schultheiss UT, Daya N, Grams ME, et al. Thyroid function, reduced kidney function and incident chronic kidney disease in a community-based population: the Atherosclerosis Risk in Communities study. *Nephrol Dial Transplant.* 2017;32(11):1874–1881.

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Care of the Human Immunodeficiency Virus–Infected End-Stage Kidney Disease Patient

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Introduction

The human immunodeficiency virus (HIV)–infected end-stage kidney disease (ESKD) patient presents specific clinical and logistical challenges to dialysis care providers. In this chapter, we discuss the shifting epidemiology and current management of ESKD in people living with HIV.

Epidemiology

Currently, the only nationally representative data regarding the incidence and prevalence of HIV infection among ESKD patients comes from United States Renal Database System (USRDS) surveillance of HIV-associated nephropathy (HIVAN) and antiretroviral prescriptions for patients enrolled in Medicare part D. Based on these data, the incidence of HIV infection in ESKD patients has plateaued, but the prevalence has continued to increase.[1] In a cohort of 38,354 HIV-infected adults in Canada and the United States, 592 (1.5%) had ESKD. The 286 individuals who developed ESKD during the 9-year study period were more likely to be Black and have a history of diabetes mellitus, hypertension, and intravenous drug use. Additionally, they were less likely to be on antiretrovirals and virologically suppressed.[2]

In the early days of the acquired immunodeficiency syndrome (AIDS) pandemic, HIVAN became a leading cause of kidney failure among HIV-infected individuals. It accounted for a third of biopsy-proven cases of kidney failure in HIV-infected persons between 1995 and 2004 and became the fourth leading cause of ESKD among Black adults between 1994 and 1998. The introduction of combination antiretroviral therapy (cART) in the mid-1990s led to a decrease in the incidence of HIVAN and comorbidities, such as diabetes mellitus, hypertension, hepatitis C virus (HCV) coinfection, intravenous drug use, and nephrotoxicity from antiretroviral agents became major risk factors for the development of ESKD among HIV-infected individuals.[2]

Improved Survival of the Human Immunodeficiency Virus-Infected End-Stage Kidney Disease Patient

One-year survival after starting dialysis in HIV-infected ESKD patients improved from 56% before 1990 to 74% in 1999.[3] In a more recent study of patients who started on dialysis due to HIVAN between 1989 and 2011, 1-year survival increased from 42% in the pre-ART era (1989–1995) to 80% in the modern ART era (2002–2011).[4] Additionally, transplantation offers 1- and 3-year survival rates of 95% and 88%, respectively.[5] These gains are attributed to the increased availability of ART and recent efforts to improve engagement across the HIV continuum of care (i.e., diagnosis, engagement and retention in care, adherence to ART, and virologic suppression). However, these gains are not uniform across all patients; in a study of HIV-infected Black Americans in Baltimore, the median survival after initiation of dialysis remained relatively stable at 19–22 months between 1989 and 2000.[6] Additionally, in a study of a national dialysis population comparing survival rates among HIV-infected, HIV and HCV coinfected, and HIV and HCV noninfected individuals, HIV infection was associated with increased mortality among non-Whites but not among Whites, whereas HIV and HCV coinfection was associated with higher mortality regardless of race.[7]

Hemodialysis and Vascular Access

The most common kidney replacement modality used in HIV-infected patients is hemodialysis. A recent study utilizing the Vascular Quality Initiative Registry between 2011 and 2018 explored arteriovenous (AV) access outcomes, including reintervention, occlusion, and mortality. Individuals with HIV undergoing AV access creation had similar outcomes compared to those without HIV.[8]

Tunneled dialysis catheter infections are associated with an increased risk of infection and a higher risk of death in HIV-infected patients.[7,9] Therefore, HIV-infected patients with chronic kidney disease (CKD) should be referred to a nephrologist early, and AV access planning should be timely.

Infection Control in Hemodialysis

In contrast to hepatitis B virus (HBV)–infected ESKD patients, HIV-infected ESKD patients do not require routine surveillance for HIV seroconversion or special isolation procedures during dialysis. HIV-infected patients may participate in dialyzer reuse programs with the reuse of the dialysis filter by the same patient.[10]

Most professional societies recommend HIV screening prior to starting dialysis primarily to identify patients who may benefit from ART. Subsequent testing for infection control (IC) purposes is not necessary.[11,12] Notably, there is an increased rate of false-positive enzyme immunoassay (EIA) and Western blot results when screening ESKD patients compared to the general population (8% versus < 1%).[13] It is unclear if this issue persists with current generation testing. Regardless, an HIV RNA viral load is always advised to follow up the results of abnormal serologic testing.

There have been at least six outbreaks of patient–patient HIV transmission in hemodialysis facilities across four countries (Argentina, Colombia, Egypt, and Saudi Arabia). All of these outbreaks occurred as a result of observed or highly suspected breaches in IC protocols.[14] These incidents underscore the importance of strict adherence to IC guidelines, emphasizing standard precautions and cleaning and disinfection of reusable dialysis equipment between patients.[10]

Health care personnel (HCP) providing dialysis services to HIV-infected patients are at risk of exposure to contaminated blood or other body fluids. The average risk of HIV transmission after a percutaneous injury is 0.3%.[15] All dialysis HCP should follow standard precautions and wear gloves whenever handling blood or other body fluids. Current Occupational Safety and Health (OSHA) regulations state that needleless systems should be in place for withdrawal of blood once venous access is established and for administration of medications and fluids. If needleless systems are not used, needles with injury-protection devices should be used. Postexposure prophylaxis (PEP) should be considered in all HCPs exposed to HIV-infected blood or other body fluids regardless of the source patient's viral load. The efficacy of PEP is highest immediately after exposure and decreases significantly if administration is delayed by ≥ 72 hours.[15] There are limited data on the presence of HIV RNA in ultrafiltrate. The HIV virion is much larger than most dialyzer membrane pores, making it unlikely to cross the dialyzer membrane into the ultrafiltrate. Despite noting a modest decrease in plasma HIV viral load after hemodialysis, one study did not detect HIV RNA in the ultrafiltrate of 10 HIV-infected ESKD patients.[16] In light of the scarcity of data, it is reasonable to consider ultrafiltrate as a contaminated body fluid after an exposure.

Peritoneal Dialysis

Peritoneal dialysis compares favorably with hemodialysis in HIV-infected patients, with similar patient survival rates.[17] From an IC standpoint, the potential for HIV transmission to dialysis HCP through contaminated blood or ultrafiltrate is not present in peritoneal dialysis. On the other hand, increased protein losses and rates of peritonitis are concerns in HIV-infected ESKD patients. In a recent series of prospective observational studies comparing 70 HIV-infected and 70 HIV-uninfected individuals on continuous ambulatory peritoneal dialysis (CAPD) over an 18-month follow-up period, mean serum albumin levels were lower in the HIV-infected cohort, and a serum albumin < 2.5 mg/dL was an independent risk factor for mortality.[18] Additionally, rates of peritonitis episodes were higher in the HIV-infected cohort (1.86 versus 0.77 episodes per person-year). HIV-infected patients were also more likely to have gram-negative peritonitis. However, catheter failure rates did not differ between the two groups.[19] In these studies, a CD4 count < 200 cells/μL was associated with increased rates of peritonitis and death. Interestingly, the higher peritonitis rates may not be due to HIV infection itself but rather to confounding variables of ethnicity, socioeconomic status, and comorbid conditions.

HIV p-24 antigen can be detected in peritoneal dialysis tubing and fluid for 3 and 7 days, respectively.[20] In a recent study, up to 10% of virologically suppressed HIV-infected patients on CAPD had detectable HIV RNA in their peritoneal dialysis fluid.[21] Therefore, peritoneal dialysis fluid should be handled as a contaminated body fluid. Peritoneal dialysis patients should be instructed to pour dialysate into the home toilet and dispose of dialysate bags and tubing by placing them in plastic bags and disposing of them into standard home trash systems.

Transplantation

Kidney transplantation (KT) for HIV-infected ESKD patients, once thought to be risky due to compounding immunosuppression, occurs routinely in the United States and globally. As stated earlier in this chapter, a 2010 prospective single-arm trial of HIV-infected ESKD patients undergoing KT revealed mean 1- and 3-year survival rates of 95% and 88%, and mean 1- and 3-year graft-survival rates of 90% and 74%. Additionally, immunosuppression did not lead

to rapid a reduction in CD4 counts. However, the 1- and 3-year rate of graft rejection was higher than anticipated at 31% and 41%, respectively.[5] Transplantation may also offer a survival benefit compared to dialysis in this population; in a retrospective study of HIV-infected ESKD patients, 5-year mortality was 79% lower for those undergoing KT compared to those remaining on dialysis.[22] Unfortunately, there are still disparities in the availability of KT for HIV-infected ESKD patients. These patients are more likely to remain on dialysis longer and less likely to remain active on the waiting list.[23]

General Dialysis Care

The Kidney Disease: Improving Global Outcomes (KDIGO) recommendations should be followed for HIV-infected ESKD patients. As noted previously, AV fistulas are preferred in these patients in order to reduce the incidence of catheter and graft infections. The goals for Kt/V, kidney osteodystrophy and anemia management, and vascular access monitoring should be followed as outlined in KDIGO. Anemia targets are in KDIGO, and different studies have demonstrated that HIV patients respond similarly to dosing of erythropoietic stimulating agents.

Nutrition and Diet

Already a problem for many ESKD patients, malnutrition can be a life-threatening condition for HIV-infected ESKD patients. Hypoalbuminemia and CD4 count < 200 cell/μL are strong predictors of mortality.[18] The management of malnutrition among HIV-infected ESKD patients is not standardized. Successful initiation of antiretroviral therapy may increase weight and should be the first step in addressing malnutrition in these patients. Aggressive dietary interventions with the assistance of a dietitian should also be initiated in any HIV-infected patient with ESKD and significant weight loss.

Other therapies that have been studied in HIV patients with malnutrition include exercise, caloric supplements, the administration of hormones, and the administration of hormonal agents. The drugs are reserved for HIV patients with documented endocrine deficiencies. Most studies using these agents have not included patients with CKD and have only demonstrated short-term benefits. In addition, the risks of these agents are significant.

Hepatitis B and C Coinfection

Due to shared routes of transmission, HIV and viral hepatitis coinfections are common. In the United States, chronic hepatitis B and C affect, on average, 14% and 20% of individuals living with HIV, respectively.[24,25]

The incidence of HBV infection in hemodialysis patients in the United States has decreased substantially from 8% in 1976 to 1% in 2002.[26] This decrease is due to increased immunization among hemodialysis center personnel and patients and implementation of various protocols for preventing nosocomial transmission, including serologic status surveillance, strict adherence to standard precautions, and isolation and use of dedicated equipment for HBV-infected patients. Deficits in cellular and humoral immunity in ESKD contribute to a suboptimal immunogenic response rate to HBV immunization. These abnormalities are augmented by HIV and HCV coinfection and CD4 count < 200 cells/μL. Only 64% of hemodialysis patients achieve immunogenicity after a standard three-dose primary series (compared to 90%–95% in the general population). The response rate may be increased by immunizing patients before they require hemodialysis and doubling the dose for patients already on hemodialysis. Some patients may also benefit from a fourth dose. Hemodialysis patients should be tested for immunogenic response 2 months after receiving the last dose of the primary series. Responders should be tested annually and receive a booster any time their HBV surface antibody decreases to < 10 mIU/mL. The primary series should be repeated in nonresponders.[10] Tenofovir, lamivudine, and emtricitabine are all active against HIV and HBV. However, lamivudine and emtricitabine have a low genetic barrier to resistance. Therefore, the preferred therapeutic regimen for HIV- and HBV-coinfected patients includes a combination of tenofovir plus either lamivudine or emtricitabine. Entecavir is another therapeutic option for HBV in patients who are already on a fully suppressive regimen for HIV.[27] Tenofovir disoproxil fumarate (TDF), lamivudine, emtricitabine, and entecavir require dose adjustment for hemodialysis patients (Table 53.1).

Transmission of HCV occurs most readily through the percutaneous route. Hemodialysis facilities should screen patients every 6 months to identify newly acquired infections. Transmission of HCV in hemodialysis facilities can be prevented by strict adherence to standard precautions and cleaning and disinfection protocols. In contrast to HBV, segregation of patients or equipment has not been shown to prevent HCV transmission.[11] Treatment of HCV appears to improve survival for hemodialysis patients.[28] The past decade has seen the introduction of direct-acting antivirals (DAAs) for the treatment of HCV with improved efficacy and tolerability compared to interferon and ribavirin. Many of these DAAs are compatible with hemodialysis. However, practitioners must be cognizant of potential drug-drug interactions between DAAs and antiretrovirals in HIV- and HCV-coinfected patients.[29]

Antiretroviral Therapy

Except for patients with certain opportunistic infections (OIs) (i.e., cryptococcal and tuberculous meningitis), ART should be started immediately or as soon as possible after HIV diagnosis regardless of CD4 count. Early initiation of ART minimizes horizontal and vertical transmission,

TABLE 53.1 Dosing of Antiretroviral Agents in Adults With Kidney Insufficiency and Hemodialysis

Drug (Abbreviation)	Standard Dosage	Dosing in Kidney Insufficiency and Hemodialysis			References
Nucleotide Reverse Transcriptase Inhibitors (NRTIs)					
Abacavir (ABC)	300 mg PO twice daily or 600 mg PO once daily	No dose adjustment necessary with kidney insufficiency or hemodialysis			Ziagen Package Insert, 06/2019
Didanosine (ddI) enteric coated (EC)	Body weight ≥ 60 kg: • 400 mg PO once daily Body weight < 60 kg: • 250 mg PO once daily	**Crcl (mL/min)** 30–59 10–29 < 10, HD, PD	**Weight ≥ 60 kg** 200 mg PO once daily 125 mg PO once daily 125 mg PO once daily	**Weight < 60 kg** 125 mg PO once daily 125 mg PO once daily 75 mg PO once daily (use pediatric suspension)	Videx EC Package Insert 11/14, Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV 2019
Emtricitabine (FTC)	200 mg PO once daily or 240 mg PO oral solution once daily	**Crcl (mL/min)** 30–49 15–29 < 15, HD	**Capsule** 200 mg PO Q48H 200 mg PO Q72H 200 mg PO Q96H	**Solution** 120 mg PO once daily 80 mg PO once daily 60 mg PO once daily	Emtriva Package Insert, 07/2012
Lamivudine (3TC)	150 mg PO twice daily or 300 mg PO once daily	**Crcl (mL/min)** 30–49 15–29 5–14 < 5, HD, PD CRRT	 150 mg PO once daily 150 mg load × 1, then 100 mg PO once daily 150 mg load × 1, then 50 mg PO once daily 50 mg load × 1, then 25 mg PO once daily 100 mg load × 1, then 50 mg PO once daily		Epivir Package Insert, 05/2019
Stavudine (d4T)	30 mg PO BID, < 60 kg 40 mg PO BID, ≥ 60 kg	**Crcl (mL/min)** 26–50 10–25, HD CRRT	**Weight ≥ 60 kg** 20 mg PO BID 20 mg PO once daily 40 mg PO once daily	**Weight < 60 kg** 15 mg PO BID 15 mg PO once daily 30 mg PO once daily	Zerit Package Insert, 12/2018
Tenofovir disoproxil fumarate (TDF)	300 mg PO once daily	**Crcl (mL/min)** 30–49 10–29 < 10, No HD HD	 300 mg PO Q48H 300 mg PO Q72–96H NOT recommended 300 mg PO every 7 days		Viread Package Insert, 12/2018
Zidovudine (AZT)	300 mg PO BID	**Crcl (mL/min)** <10, HD, PD CRRT	 100 mg PO Q8H or 300 mg PO once daily 300 mg PO BID		Retrovir Package Insert, 09/2008
Fixed Dose Combinations (NRTIs)					
Cimduo, Temixys (lamivudine + tenofovir disoproxil fumarate)	One tablet PO once daily	**Crcl (mL/min)** <50	 Combination drug not recommended		Cimudo Package Insert, 02/2018
Combivir (lamivudine + zidovudine)	One tablet PO BID	**Crcl (mL/min)** <50	 Combination drug not recommended		Combivir Package Insert, 02/2017

TABLE 53.1 Dosing of Antiretroviral Agents in Adults With Kidney Insufficiency and Hemodialysis—cont'd

Drug (Abbreviation)	Standard Dosage	Dosing in Kidney Insufficiency and Hemodialysis		References
Descovy (emtricitabine + tenofovir alafenamide)	One tablet PO once daily	**CrCl (mL/min)**		Descovy Package Insert, 01/2020
		<30, No HD	Combination drug not recommended	
		<30, HD	One tablet PO once daily	
Epzicom, Kivexa (abacavir + lamivudine)	One tablet PO once daily	**CrCl (mL/min)**		Epzicom Package Insert, 05/2019
		<50	Combination drug not recommended	
Trizivir (abacavir + lamivudine + zidovudine)	One tablet PO BID	**CrCl (mL/min)**		Trizivir Packet Insert, 05/2019
		<50	Combination drug not recommended	
Truvada (emtricitabine + tenofovir disoproxil fumarate)	One tablet PO once daily	**CrCl (mL/min)**		Truvada Package Insert, 06/2020
		30–49	One tablet PO Q48H	
		<30 or HD	Combination drug not recommended	
Non–Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)				
Delavirdine (DLV)	400 mg PO TID	No dose adjustment necessary with kidney insufficiency or hemodialysis		Rescriptor Package Insert, 08/2019
Doravirine (DOR)	100 mg PO once daily 100 mg PO BID (if given with rifabutin)	No dose adjustment necessary with mild, moderate, or severe kidney insufficiency. This drug has not been studied in ESKD and dialysis		Pifeltro Package Insert, 10/2019
Efavirenz (EFV)	600 mg PO once daily (at bedtime)	No dose adjustment necessary with kidney insufficiency or hemodialysis		Sustiva Package Insert, 10/2019
Etravirine (ETR)	200 mg PO BID	No dose adjustment necessary with kidney insufficiency or hemodialysis		Intelence Package Insert, 10/2011
Nevirapine (NVP)	200 mg PO once daily × 14 days followed by 200 mg PO BID or 400 mg PO once daily	No dose adjustment necessary with kidney insufficiency. In patients undergoing chronic HD, an additional 200 mg dose following each dialysis treatment is indicated.		Viramune Packet Insert, 10/2019
Rilpivirine (RPV)	25 mg PO once daily	No dose adjustment is required in patients with mild or moderate kidney impairment or hemodialysis. For severe kidney impairment, the patient should be monitored for increased adverse effects		Edurant Package Insert, 08/2015
Fixed Dose Combinations (NNRTI-based regimens)				
Atripla (efavirenz + emtricitabine + tenofovir disoproxil fumarate)	One tablet PO once daily	**CrCl (mL/min)**		Atripla Package Insert, 10/2019
		<50	Combination drug not recommended	
Complera (rilpivirine + emtricitabine + tenofovir disoproxil fumarate)	One tablet PO once daily	**CrCl (mL/min)**		Complera Package Insert, 02/2016
		<50, HD	Combination drug not recommended	

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TABLE 53.1 Dosing of Antiretroviral Agents in Adults With Kidney Insufficiency and Hemodialysis—cont'd

Drug (Abbreviation)	Standard Dosage	Dosing in Kidney Insufficiency and Hemodialysis		References
Delstrigo (doravirine + lamivudine + tenofovir disoproxil fumarate)	One tablet PO once daily	**CrCl (mL/min)** <50	Combination drug not recommended	Delstrigo Package Insert, 08/2018
Odefsey (rilpivirine + emtricitabine + tenofovir alafenamide)	One tablet PO once daily	**CrCl (mL/min)** <30, no HD <30, HD	Combination drug not recommended One tablet PO once daily	Odefsey Package Insert, 12/2019
Symfi, Symfi Lo (efavirenz + lamivudine + tenofovir disoproxil fumarate)	One tablet PO once daily	**CrCl (mL/min)** <50 or HD	Combination drug not recommended	Symfi Lo Package Insert, 02/2018
Protease Inhibitors (PIs)				
Atazanavir (ATV)	400 mg PO once daily (unboosted) 300 mg PO once daily with ritonavir	No dose adjustment necessary with kidney insufficiency. Treatment naïve patients on HD: 300 mg PO once daily + ritonavir Treatment experienced patients on HD: not recommended		Reyataz Package Insert, 03/2018
Darunavir (DRV)	No darunavir resistance: 800 mg PO once daily (with ritonavir) 1+ darunavir resistance or unknown: 600 mg PO BID (with ritonavir)	No dose adjustment necessary with kidney insufficiency or hemodialysis		Prezista Package Insert, 12/2011
Fosamprenavir (FPV)	1400 mg PO once daily with ritonavir (treatment naïve) 700 mg PO BID with ritonavir (treatment experienced)	No dose adjustment necessary with kidney insufficiency or hemodialysis		Lexiva Package Insert, 09/2009
Nelfinavir (NFV)	1250 mg PO BID	No dose adjustment necessary with kidney insufficiency or hemodialysis; however, use is not recommended in this population		Viracept Package Insert, 04/2012
Indinavir (IDV)	800 mg PO BID with ritonavir	No dose adjustment necessary with kidney insufficiency or hemodialysis; however, use is not recommended in this population		Crixivan Package Insert, 06/2008
Saquinavir (SQV)	1000 mg PO BID with ritonavir 2000 mg PO once daily with ritonavir (treatment naïve)	No dose adjustment necessary with kidney insufficiency or hemodialysis; however, data is limited		Invirase Package Insert, 04/2010
Tipranavir (TPV)	500 mg PO BID with ritonavir	No dose adjustment necessary with kidney insufficiency or hemodialysis; however, data is limited		Aptivus Package Insert, 06/2020

TABLE 53.1 Dosing of Antiretroviral Agents in Adults With Kidney Insufficiency and Hemodialysis—cont'd

Drug (Abbreviation)	Standard Dosage	Dosing in Kidney Insufficiency and Hemodialysis	References
Fixed Dose Combinations (PI-based regimens)			
Evotaz (atazanavir + cobicistat)	One tablet PO once daily	Not recommended in treatment-experienced patients who have end-stage kidney disease managed with hemodialysis	Evotaz Package Insert, 07/2020
Kaletra (lopinavir + ritonavir)	Two tablets PO BID	No dose adjustment necessary with kidney insufficiency or hemodialysis; however, data is limited	Kaletra Package Insert, 06/2010
Prezcobix (darunavir + cobicistat)	One tablet PO once daily	No dose adjustment necessary with kidney insufficiency or hemodialysis; however, do not coadminister with TDF if CrCl < 70	Prezcobix Package Insert, 01/2015
Symtuza (darunavir + cobicistat + emtricitabine + tenofovir alafenamide)	One tablet PO once daily	**CrCl (mL/min)** <30 or HD — Combination drug not recommended	Symtuza Packet Insert, 07/2018
Integrase Inhibitors (INSTIs)			
Dolutegravir (DTG)	50 mg PO once daily 50 mg PO BID if INSTI mutation or drug interaction	No dose adjustment necessary with kidney insufficiency, although use caution in INSTI experienced patients with ESKD. Dolutegravir has not been studied in dialysis	Tivicay Package Insert, 08/2013
Raltegravir (RAL)	400 mg PO BID 800 mg PO BID if given with rifampin	No dose adjustment necessary with kidney insufficiency or hemodialysis	Isentress Package Insert, 08/2013
Fixed Dose Combinations (INSTI-Based Regimens)			
Biktarvy (bictegravir + emtrictabine + tenofovir alafenamide)	One tablet PO once daily	**CrCl (mL/min)** <30 — Combination drug not recommended	Biktarvy Package Insert, 02/2018
Dovato (dolutegravir + lamivudine)	One tablet PO once daily	**CrCl (mL/min)** <50 — Combination drug not recommended	Dovato Package Insert, 08/2020
Genvoya (elvitegravir + cobicistat + emtricitabine + tenofovir alafenamide)	One tablet PO once daily	**CrCl (mL/min)** <30, no HD — Combination drug not recommended <30 on HD — No dose adjustment required	Genvoya Package Insert, 02/2019
Juluca (dolutegravir + rilpivirine)	One tablet PO once daily	No dose adjustment necessary with kidney insufficiency or hemodialysis; however, monitor for adverse effects with CrCl <30	Juluca Package Insert, 07/2020
Stribild (elvitegravir + cobicistat + emtricitabine + tenofovir disoproxil fumarate)	One tablet PO once daily	**CrCl (mL/min)** <70 — Do not initiate combination drug <50 — Combination drug not recommended	Stribild Package Insert, 08/2012

Continued

TABLE 53.1 Dosing of Antiretroviral Agents in Adults With Kidney Insufficiency and Hemodialysis—cont'd

Drug (Abbreviation)	Standard Dosage	Dosing in Kidney Insufficiency and Hemodialysis	References
Triumeq (dolutegravir + abacavir + lamivudine)	One tablet PO once daily	**Crcl (mL/min)** <50 Combination drug not recommended	Triumeq Package Insert, 03/2020
CCR5 Antagonist			
Maraviroc (MVC)	150 mg PO BID if given with potent CYP3A inhibitor 300 mg PO BID if no interacting medication 600 mg PO BID if given with potent CYP3A inducer	Not recommended with potent CYP3A inhibitor or inducer with kidney impairment or dialysis	Selzentry Package Insert, 08/2007
Fusion Inhibitor			
Enfuvirtide (T20)	90 mg subcutaneous BID	No dose adjustment necessary with kidney insufficiency or hemodialysis	Fuzeon Package Insert, 12/2019
CD4 Attachment Inhibitor			
Ibalizumab-uiyk	2 g IV × 1, then 800 mg IV every 2 weeks	No dose adjustment necessary with kidney insufficiency. This medication has not been studied in dialysis patients	Trogarzo Package Insert, 03/2018

Crcl, creatinine clearance; *CRRT*, continuous renal replacement therapy; *ESKD*, end-stage kidney disease; *HD*, hemodialysis; *PD*, peritoneal dialysis.

promotes faster CD4 count recovery and decreases morbidity and mortality from adverse infectious and noninfectious events.[30] HIV-infected individuals are several times more likely to have proteinuria than the general population and, as a result, are more likely to develop cardiovascular events and mortality. Use of ART and virologic suppression has been shown to improve proteinuria.[31] Lastly, in an analysis of participants from the START trial, patients in the early-ART group had a modest decrease in the risk of developing proteinuria compared to those in the delayed-ART group (RR, 0.74; 95% CI, 0.55–1.00; $p = 0.049$).[32]

Of the commonly prescribed antiretroviral agents, tenofovir is recognized for a broad spectrum of potential nephrotoxicity that includes proximal tubular dysfunction that may rarely progress to Fanconi syndrome, acute kidney injury (AKI), and CKD. Both TDF and tenofovir alafenamide (TAF) are hydrolyzed to tenofovir before being phosphorylated to tenofovir diphosphate, a competitive inhibitor of HIV reverse transcriptase. The difference is that TDF is hydrolyzed extracellularly, whereas TAF is hydrolyzed intracellularly, which results in decreased accumulation of tenofovir in the proximal tubules and therefore decreased nephrotoxicity.[33] The protease inhibitors (PIs) atazanavir and indinavir are associated with nephrolithiasis, AKI, and CKD.[31] However, these agents have been mostly replaced by integrase strand transfer inhibitors (INSTIs). There are case reports of rhabdomyolysis and AKI due to raltegravir.[34] Dolutegravir can cause modest increases in creatinine by inhibiting creatinine secretion by kidney transport proteins without truly decreasing glomerular filtration.[31] Several antiretrovirals are eliminated primarily through the kidneys and require dose adjustments in hemodialysis patients (see Table 53.1). In general, nucleoside reverse transcriptase inhibitors (NRTIs) and atazanavir require dose adjustment in hemodialysis patients. Non-NRTIs (i.e., efavirenz and rilpivirine), darunavir, another PI, and INSTIs (dolutegravir and raltegravir) do not.[30] Unfortunately, most single-tablet regimens (STRs) contain lamivudine or tenofovir and, therefore, must be split into their components for hemodialysis patients. The recently introduced two-drug STR dolutegravir-rilpivirine does not require dose adjustment for kidney insufficiency; however, it has not been widely studied in this population.

Opportunistic Infection Prophylaxis and Immunizations

In the 1980s, the use of OI chemoprophylaxis and immunizations decreased morbidity and mortality in patients living with AIDS. Azithromycin used for *Mycobacterium avium* intracellular (MAI) prophylaxis does not require dose adjustment for kidney insufficiency. Trimethoprim-sulfamethoxazole may be dose adjusted for hemodialysis. Immunization recommendations for

HIV-infected and ESKD patients overlap for the most part. HIV-infected patients also require meningococcal vaccination.[30]

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Recommended Reading

CDC Dialysis Safety | Guidelines, recommendations, and resources. Accessed July 28, 2020. https://www.cdc.gov/dialysis/guidelines/index.html.

Recommendations regarding infection prevention practices and immunizations for ESKD patients on hemodialysis and peritoneal dialysis.

AIDS Info | Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Accessed July 30, 2020. https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/.

Recommendations for management of HIV. Has a section for specific considerations in HIV-infected ESKD patients and recommendations for kidney dosing of antiretrovirals.

American Association for the Study of Liver Diseases | HCV guidance: recommendations for testing, managing, and treating hepatitis C. Accessed July 30, 2020. https://www.hcvguidelines.org/.

Recommendations for management of HIV. Has a section for specific considerations in HIV-infected ESKD patients and recommendations for kidney dosing of antiretrovirals.

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COVID-19 and Dialysis Patients

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The Impact of COVID-19 on Outpatient Dialysis Facilities

Introduction

This is a point-in-time view of early pandemic. While the principles remain the same, the facts of COVID-19 care have evolved since 2020. Through August 2020, COVID-19 disease caused by the novel coronavirus SARS-CoV-2 has infected more than 30,500,000 people worldwide and caused nearly 1,000,000 deaths. The virus enters host cells via angiotensin-converting enzyme 2 (ACE-2) receptors, highly expressed in the mouth, tongue, and lower lung types I and II alveolar epithelial cells. ACE-2 receptors are expressed in target organs for SARS-CoV-2, including kidney proximal tubular cells and podocytes, cardiac endothelial cells, gut enterocytes, and blood vessels. Inhibitors of the renin-angiotensin system are common treatments for hypertension in patients with chronic kidney disease (CKD). While initial studies suggested that these agents might increase ACE-2 receptor expression, data do not support an association with COVID-19. Several possible mechanisms have been proposed for acute kidney injury (AKI) in the setting of COVID-19 infection, including prerenal injury resulting from high fever, gastrointestinal (GI) losses, and decreased oral intake; cardiac complications like cardiomyopathy or cardiorenal syndrome leading to renal hypoperfusion; toxic tubular damage due to intense production of proinflammatory cytokines leading to decreased renal perfusion and tubular injury over time; direct viral entry into kidney cells leading to tubular damage; and a hypercoagulable state leading to thrombotic microangiopathy.

Published reports document risk factors for COVID-19 infection, including hypertension (odds ratio [OR], 2.29), diabetes mellitus (OR, 2.47), and cardiovascular disease (OR, 2.93), all of which are common among patients with CKD. Increasing age, obesity, and the black race also increase the risk of infection. Minorities and older patients are disproportionately represented in the population of patients with CKD: 23% of incident patients are older than 75, 26% are black, and 15% are Hispanic. Patients requiring maintenance dialysis have a much higher rate of infection when treated by in-center hemodialysis (HD) compared to home dialysis therapies. The risk of mortality increases as CKD progresses; 15%–40% of patients with CKD requiring maintenance dialysis who are infected by COVID-19 die. Mortality is greater in those with hypertension, diabetes mellitus, and cardiovascular disease, as well as older and black patients.

Initial symptoms of COVID-19 may be milder in patients with CKD: fatigue, cough, and dyspnea are reported less frequently; hypoxemia is less apparent because of reduced oxygen levels at baseline, and fever is less common because of reduced baseline body temperature. Diarrhea and fatigue are more common in patients with CKD. Many patients present asymptomatically for HD but develop a fever during treatment and are subsequently diagnosed with COVID-19. Patients with CKD have higher levels of creatine kinase, myoglobin, troponin I, B-type natriuretic peptide, and procalcitonin than those with normal kidney function.

The impact of COVID-19 on the population of patients receiving maintenance dialysis is not yet known: will the high mortality rate be balanced by the number who initiate renal replacement therapy (RRT) as a result of AKI associated with COVID-19? Similarly, the impact of COVID-19 on the nephrology workforce is not yet known; some will retire because of the physical and emotional impact of COVID-19, but new personnel may be attracted by the opportunities the field presents to care for patients with chronic illness throughout their life cycle and the opportunity to impact the outcomes of patients with severe acute illness.

Patients

A major tool to prevent infection spread during the SARS-CoV-2 pandemic is social distancing. Maintaining at least 6 ft of separation between individuals is virtually impossible for patients receiving in-center HD, where they are often tightly clustered at the dialysis center and during transportation from home. In spite of the risk, patients must continue to receive life-sustaining dialysis treatments. Infection "hotspots" developed early during the COVID-19 pandemic in New York, Chicago, Detroit, and other cities. Hospitals

were quickly overwhelmed, precluding the possibility of sending patients with suspected or confirmed COVID-19 and mild symptoms to the hospital for dialysis management. Patients with known SARS-CoV-2 infection or those suspected to be infected (patients under investigation or PUIs) had to be treated in the outpatient setting. Some centers shortened dialysis treatments or decreased their frequency to minimize the risk of no social distancing, but concerns arose quickly about the risk of adverse outcomes of reduced dialysis adequacy. Exposure to COVID-19 was reduced by furlough of infected staff and by cohorting infected patients and PUIs in facilities treating only patients with active or suspected infection or on separate shifts caring for only infected or PUI patients. If neither option was available, the Centers for Disease Control and Prevention (CDC) advised treating such patients at the end of a row or in a corner of the dialysis facility separated from noninfected patients by at least 6 ft. Most dialysis centers adopted policies for patients to phone in before arrival if they had symptoms suggestive of infection. Patients are screened on arrival with temperature measurement and screening questions about symptoms and possible exposure. Waiting rooms are largely unused, and patients are asked to remain in their cars when possible and come directly to the dialysis station when it is ready for their arrival. Any patients who screen positive are separated from all others.

The timing of the safe return of patients to the dialysis center after SARS-CoV-2 infection symptoms are gone remains a challenge. Widespread limits on availability of reverse transcriptase-polymerase chain reaction (rt-PCR) testing for COVID-19 made it difficult to decide when patients are no longer shedding virus or viral particles. CDC guidance suggested that infected patients who have recovered from the symptoms of COVID-19 may return to the general dialysis population after two negative rt-PCR tests separated by at least 48 hours. An alternative time-based strategy permitted return 10–20 days after a positive test in the absence of symptoms. However, dialysis patients recovering from COVID-19 often continue to have positive tests for weeks or even months. Since the presence of detectable viral RNA does not necessarily indicate infectivity, these patients with persistently positive rt-PCR created confusion in this vulnerable population. While patients with normal kidney function recovering from COVID-19 are no longer infective 9–10 days after symptoms first appear, even if they have detectable viral RNA in their nasopharynx, it is not clear that the same can be said for dialysis patients, many of whom have impaired immune response systems. For this reason, the CDC eliminated its suggestion for postinfection viral testing and now advises using only the time-based method to determine when recovered patients can return to the general dialysis population. Antibody tests indicate prior exposure to the virus, but their exact meaning is not yet clear. Although some antibody tests are positive in 15%–20% of patients without known COVID-19 infection, the high prevalence of asymptomatic infection makes it difficult to interpret this finding. Vaccines against SARS-CoV-2 are expected to be widely available in 2021. Given the impact of COVID-19 on patients with CKD, it is essential that their safety and efficacy be tested in this population. Once vaccines are proven safe and effective, patients with CKD and those caring for them must be given priority for vaccination.

Anxiety and emotional stress increased in dialysis patients during the COVID-19 pandemic. All dialysis patients, those infected, and those fearing infection may suffer from debilitating psychological distress. Tools to manage these symptoms include individual counseling and group sessions using electronic communication tools. Creative solutions, such as telehealth visits from social workers, dieticians, and for many needs, physicians, were used in outpatient dialysis centers. A waiver from the Centers for Medicare and Medicaid Services (CMS) during the public health emergency (PHE) permitted use of telehealth for monthly capitation visits. Telehealth may also be useful for patient and family education about home dialysis and transplant options and initial evaluations.

Because of the large number of patients suffering a critical illness as a result of acute respiratory distress syndrome (ARDS) associated with COVID-19 infections, attention turned to potential shortages of life-sustaining equipment like ventilators. While increasing the supply of available ventilators was the first priority, serious discussions were held about rationing them if the patient need exceeded the available supply. Policymakers considered guidelines for allocating ventilators; the State of Alabama Emergency Operations Plan stated that patients with end-stage organ failure, including anyone requiring dialysis, not receive ventilator support. The U.S. Department of Health and Human Services (HHS) Office of Civil Rights resolved a compliance review, and a revision removed this guideline. Recommendations are for a nuanced approach to rationing limited resources without arbitrarily excluding individuals.

Staff

Dedicated professionals care for patients with CKD every day; the COVID-19 pandemic changed the paradigm dramatically. Dialysis nurses and technicians are the major heroes, daily caring for in-center patients despite the risk to themselves and their families. Other staff, including physicians, social workers, dieticians, and administrators, were encouraged to have less direct patient contact and use telemedicine or telephonic contact in some instances. Strict use of hand hygiene and personal protective equipment (PPE), including gloves, masks, gowns, and eye-protective shields or goggles, proved effective in preventing viral transmission. Early pandemic reports from Europe of viral spread among patients and between staff and patients were largely eliminated after widespread measures were used to detect infection and isolate PUIs. As some staff became ill and had to stay away on sick leave, the higher workload on those remaining was particularly stressful with the restrictions imposed by screening and PPE procedures. These critical staff who remain often are faced with a very difficult decision:

to accept the risk of exposing themselves and their loved ones to a potentially fatal illness or to risk loss of salary and benefits and the psychological stress of turning away from critical needs if they decide to leave work. This dilemma places stress and anxiety on all staff and their families. Staff needs to be wary of subtle signs of COVID-19 infection while at the same time helping patients manage their physical and emotional symptoms. Staff had to learn to employ PPE and conduct their routine activities while attired with face shields, masks, gloves changed frequently, and isolation gowns.

At the same time, community-wide recognition of the valuable contributions of health care workers and enhanced relationships with colleagues and patients empowered those who worked through the pandemic. Many have shared that their self-value and confidence and pride blossomed during the pandemic, providing an opportunity to give to their community as never before. While some staff have elected early retirement, we believe that many young people may be inspired by staff heroism to choose health care professions.

Administrators

Dialysis facility administrators faced a crisis from the moment the first case of COVID-19 was diagnosed in a patient with CKD; spread mitigation had to be balanced with safety of patients and staff in the face of challenging circumstances, including national shortages of PPE. Schedules had to be retooled to allow physical distancing for patients awaiting treatment and staff during meal breaks. Community spread of COVID-19 led to staff absences for quarantine and illness, increasing the stress on the system.

Meeting social distancing requirements proved to be a substantial challenge for many administrators. While large dialysis organizations designated facilities to treat infected patients or PUIs, smaller organizations were rarely able to do so. This led to the designation of sections of a facility or shifts for patients with known or suspected infection. Using less densely crowded shifts, i.e., the last shift on Tuesday, Thursday, and Saturday allowed for the greatest separation. Some facilities were retooled to provide plexiglass shields outside the treatment area and to create greater space in other areas where patients might congregate, such as waiting areas.

At points during the COVID-19 crisis, concerns arose regarding the supply chain for PPE, dialyzers, and dialysis fluids. Fortunately, suppliers were able to keep up with demand, and shortages were addressed before crises arose. Dialyzer shortage never reached crisis proportions.

Protocols to mitigate the risk of infection spread in dialysis facilities included screening everyone entering the facility for signs of infection, known exposure, travel to areas with a high risk of community spread, fever, new cough, or shortness of breath. Everyone in the facility must wear a mask, and hand hygiene is essential. Because testing availability was limited and results were delayed, it was not practical to test everyone on a regular basis. The CDC recommends use of standard disinfection protocols to clean the dialysis station between patients, but many facilities expanded disinfection protocols to include all touch surfaces in addition to those exposed to blood or body fluids during dialysis treatment.

Recognizing the impact of the PHE on dialysis facilities, CMS waived the requirements for data submission to the CrownWeb National ESRD Patient Registry and Quality Measure Reporting System and the ESRD Quality Incentive Program during the PHE. Facilities were permitted to opt out of the Spring 2020 In-Center Hemodialysis Consumer Assessment of Healthcare Providers and Systems because of the impact of the PHE on facilities. These waivers permitted administrators to focus attention on patient care and safety.

Home Dialysis

Compared to international rates of 30%–80%, only 10% of U.S. dialysis patients are treated by home dialysis modalities. During the COVID-19 pandemic, benefits of home dialysis increased, patients did not need treatment in dialysis facilities, and treatment prescriptions can be modified based on individual patient needs. Home dialysis patients, able to shelter at home, had lower infection rates than in-center patients.

Temporary regulatory waivers issued by CMS during the PHE provided opportunities to employ technology in unprecedented ways. CMS waived the requirement for a monthly in-person visit for home dialysis patients deemed stable by the treating nephrologist. Prior to the PHE, the first three monthly visits and one visit each quarter were required to be conducted in person; these requirements were waived during the PHE. Waivers were issued related to the requirement for initiation of telehealth. The Office of Civil Rights of the HHS notified health care providers that they would employ discretion and impose no penalties under the Health Insurance Portability and Accountability Act of 1996 as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 for the use of common electronic technologies for telehealth. These waivers greatly expanded the availability of telehealth to patients treated by home dialysis, emphasizing the benefits of home dialysis.

Coupled with the Advancing American Kidney Health Initiative announced by President Trump on July 10, 2019, the apparent benefits of home dialysis during the PHE further stimulated interest in home dialysis. Large dialysis organizations report a 10%–15% increase in the use of home modalities during the first 3 months of the pandemic. The anticipated unprecedented growth in home dialysis demands parallel growth in the workforce. Trainees must be afforded experience caring for patients managed by home dialysis; some suggest offering an additional 12 months of training dedicated to home dialysis if such programs can be funded. The COVID-19 pandemic demonstrated the inadequacy of the current nursing workforce: hospitals starting acute peritoneal dialysis (APD) programs struggled to find

nurses skilled in PD. The nationwide nursing shortage is especially acute in nephrology and more so for home dialysis therapies. Some suggest training patient care technicians to support nephrology nurses. Relatively few surgeons have experience successfully placing PD catheters; some interventional radiologists insert catheters, but payment is insufficient to induce more to learn the procedure.

Issues arose regarding home dialysis training during the PHE: patients typically spend 2–3 weeks undergoing face-to-face education about dialysis technique, monitoring of daily health, and troubleshooting before they can perform PD independently. Home HD training takes 4–8 weeks of face-to-face education. During the PHE, some programs developed virtual curricula and used telemedicine in place of hands-on training.

Some issues arose related to the delivery of supplies to home patients. Masks were in short supply, but facilities were able to reach into their own supplies to meet the demand. Some delivery services, reluctant to enter patient homes fearing exposure to infection, left supplies outside of patient homes. In some cases, dialysis facilities had to complete deliveries to permit patients to continue their dialysis treatments. These challenges were largely resolved with training and adequate PPE.

Some patients who initiate dialysis during a hospital admission are treated by PD; this number increases during the PHE. As patients recovered from their infections, they received education from hospital nurses. However, few rehabilitation facilities perform PD, and CMS regulations do not pay for PD training for patients with AKI. Thus, some patients treated in-hospital with PD for AKI were switched to HD before discharge to an outpatient dialysis facility.

The Impact of COVID-19 on Inpatient Dialysis Facilities

Acute Kidney Injury and Patient Volume

Early in the pandemic, reports from China showed that 40% of patients hospitalized with SARS-CoV-2 infection had hematuria or proteinuria, and 20% had a decline in kidney function. AKI was reported widely as the pandemic spread, affecting approximately 30% of infected patients who were hospitalized. RRT is required by about 6% of hospitalized COVID-19 patients. Among patients requiring care in intensive care units (ICUs), up to 68% require RRT. AKI and especially the need for RRT are significant predictors of mortality. Risk factors for the development of AKI include severe COVID disease, requirement for mechanical ventilation and vasopressors, increased age, male sex, black race, higher body mass index (BMI), and comorbidities including diabetes mellitus, hypertension, and cardiovascular disease. AKI is threefold more common in patients with preexisting kidney disease.

When the pandemic exploded in cities like New York, Chicago, Detroit, and New Orleans, dialysis resources were severely stressed. The volume of patients with AKI requiring RRT and CKD requiring dialysis in the hospital required up to 5 times the usual supplies of dialysis fluid and other supplies and, in some cases, threatened to overwhelm facilities' capacity to provide dialysis. Many patients were managed in isolation settings, requiring treatments to be delivered by a dedicated nurse. Issues of risk exposure for patient care staff further complicated the administration of dialysis treatments. Dialysis personnel shortages severely stressed the system: the perfect storm of dialysis nurses who became infected or were exposed to infection required furlough from work, the increase in demand for dialysis care required working dialysis staff to increase their days and hours of work, created a personnel crisis solved by the heroic work of ICU, and dialysis nurses and additional personnel responding to a crisis call to come to hotspots and offer assistance.

While indications for initiation of RRT are no different for patients with COVID-19 with underlying AKI than for other patients with AKI, some used convective therapies and other extracorporeal therapies with a goal of removing proinflammatory cytokines from patients suffering from cytokine storm. There are inadequate data to confirm the benefits of these treatments.

Continuous Renal Replacement Therapy

Continuous RRT (CRRT) is the preferred treatment for hemodynamically unstable critically ill patients who require RRT. There are inadequate data to define an optimal CRRT prescription. Patients with COVID-19 infections, particularly those with cytokine storm, are frequently hypercoagulable. Numerous reports document higher rates of clotting of CRRT circuits in patients with COVID-19, resulting in increased nursing workload and increased replacement of CRRT filters, increasing use of potentially scarce resources. Regional citrate anticoagulation may be more efficacious in preventing clotting, but citrate may not be metabolized by patients with severe liver failure or shock. Heparin and argatroban are well-established alternative agents that improve filter life. Strategies to maintain equipment outside the patient room were employed to limit staff exposure to infection. However, this required long blood lines, causing possible cooling of circuit blood and higher return pressure leading to blood loss.

In summary, the unprecedented need for CRRT during the pandemic risked a shortage of supplies, including machines, filters, fluid, and appropriately trained staff. Care teams responded to these shortages by considering alternative renal replacement strategies, including slow, low-efficiency hemodialysis (SLED), prolonged intermittent RRT (PIRRT), and APD.

Addressing Supply Shortages

Lactate-Based Continuous Renal Replacement Therapy

In patients with AKI, metabolic acidosis, associated with poor prognosis, is treated by alkali infusion during CRRT.

Acetate or lactate can be used to provide alkali but must be metabolized to bicarbonate by the liver; data show comparable survival and acid-base control. Acetate solutions are recommended by Kidney Disease: Improving Global Outcomes (KDIGO) guidelines because of concerns regarding hyperlactatemia leading to cardiodepression, but some data show better cardiac function with lactate. During the COVID-19 pandemic, acetate-based CRRT fluids were in short supply; manufacturers offered lactate-based solutions to fill the void. Despite concerns, these fluids were used in some cases without apparent increased adverse events.

Homemade Continuous Renal Replacement Therapy Solutions

Commercially prepared sterile CRRT fluid requires careful monitoring of potassium and magnesium levels. CRRT fluid can be manufactured at the hospital level but is prone to human error, which can lead to significant electrolyte derangements. During the pandemic, when CRRT fluid shortages required creative ways to ensure adequate supplies to deliver RRT to all who needed it, several organizations manufactured their own CRRT solutions. Using standard volumetric single-pass dialysis machines with acid and bicarbonate concentrates and reverse osmosis product water, these hospitals produced fluid identical to standard dialysate used for intermittent HD. In consultation with the Food and Drug Administration (FDA), these organizations ran dialysate through a standard hemodialyzer to create ultrapure solution, which was collected into 6–8-L bags. Fluid was tested regularly to ensure it met Association for Advancement of Medical Instrumentation (AAMI) ultrapure standards for microbial counts (< 0.1 CFU/mL) and endotoxin concentration (< 0.03 UE/mL). These solutions were then used to provide CRRT. There were no apparent problems or complications, suggesting the safety, efficacy, and cost-effectiveness of this PHE-required process. It is important to note that FDA guidance requires that such noncommercial fluids be used as dialysate, not infusate, and be used within 4–24 hours of production. These noncommercial solutions should be used only locally and not be shipped elsewhere to avoid possible compositional deterioration.

Prolonged Intermittent Renal Replacement Therapy

Prolonged intermittent RRT (PIRRT) treatments last between 8 and 16 hours three to five times weekly. These regimens provide solute clearance and ultrafiltration intermediate between intermittent HD and CRRT. PIRRT is provided with the same equipment as CRRT. Randomized trials of patients with AKI have failed to show differences between CRRT, PIRRT, and intermittent HD in terms of mortality or recovery of kidney function. During the COVID-19 pandemic, machines capable of slow dialysis therapies were in short supply. PIRRT was used to control volume and electrolytes and to allow sharing of one machine among two to three patients. Addressing the machine shortage required increased use of disposable dialysis supplies but allowed all patients to receive a minimum sufficient dose of dialysis.

Acute Peritoneal Dialysis

Prior to the advent of CRRT machines with blood pumps, APD was a common treatment for AKI. As intermittent HD and CRRT replaced APD treatment for AKI, fewer hospital nurses maintained competency with APD, and its popularity waned. Some data comparing APD to CRRT show better survival with APD with fewer infections, shorter ICU stay, and better renal recovery. During the COVID-19 pandemic, with shortages of CRRT machines, supplies, and trained nurses, alternative RRT modalities were required. Some turned to APD, in addition to PIRRT and standard intermittent HD, to fill the need. While many patients with AKI are good candidates for APD, others are not. Patients with abdominal scars, uncorrected hernias, high likelihood of prone ventilation, active GI issues, dual antiplatelet therapy, or BMI > 30 have relative contraindications for APD. In addition, patients who are highly catabolic and those with high fluid removal requirements may be better served with hemo-based RRT. More than 25% of screened patients were deemed suitable candidates using these criteria. Double-cuff tunneled PD catheters were placed at the bedside, and APD was started within 24 hours of placement. Patients could be treated by automated or manual PD. Initial dwell volumes should start at 750 mL and increase in 500 mL increments every 48–72 hours until a goal of 2000 mL is reached. No catheter leaks or bleeding were detected, and adequate control of electrolytes and volume was achieved in all patients following this protocol.

In summary, the COVID-19 pandemic has shown that dialysis patients are particularly vulnerable to infection and have a high mortality rate. AKI among patients with and without preexisting kidney disease is surprisingly common, increasing the need for RRT. During surges in infection, care teams have demonstrated creativity in utilizing multiple RRT modalities and even by manufacturing their own dialysate solutions. Staff shortages induced by staff illness and increased demand have been major stressors on the ability to deliver RRT to all who need it, but heroic, sustained work by ICU and dialysis staff has saved thousands of lives. Mental health is stressed in patients and staff during a pandemic, and resources to help alleviate this is required. Home dialysis is particularly attractive in times of community virus transmission and social distancing. In-hospital PD has seen a resurgence for AKI and may also increase PD treatment for ESKD. Lessons learned from locations affected by COVID-19 early in the pandemic offer important lessons regarding best outpatient dialysis facility management, inpatient RRT preparedness, and best management of patients returning to the dialysis facility from the hospital after recovery from COVID-19.

Suggested Reading

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This paper describes issues with clotting in patients with COVID-19 and the clinical consequences thereof.

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This trial compares the results of peritoneal dialysis and continuous dialysis therapies used in patients with AKI complicating critical illness.

Corbett RW, Blakey S, Nitsch D, et al. Epidemiology of COVID-19 in an urban dialysis center. *J Am Soc Nephrol.* 2020 Aug;31(8):1815–1823.

This paper describes patterns of COVID-19 infection in an urban dialysis center in a hotspot at the height of the pandemic.

Goldfarb DS, Benstein JA, Zhdanova O, et al. Impending shortages of kidney replacement therapy for COVID-19 patients. *Clin J Am Soc Nephrol.* 2020;15(6):8800–8882.

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Heering P, Ivens K, Thumer O, et al. The use of different buffers during continuous hemofiltration in critically ill patients with acute renal failure. *Intensive Care Med.* 1999;25:1244–1251.

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This paper describes use of PD for AKI complicating COVID-19 infection in the United States.

Tandukar S, Palevsky PM. Continuous renal replacement therapy: who, when, why, and how. *Chest.* 2019;155(3):626–638.

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Psychosocial Issues in Patients Treated With Dialysis

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This chapter reviews the growing scientific literature on the psychosocial challenges patients with end-stage renal disease (ESRD) treated with hemodialysis (HD) confront, concentrating on psychopathology, sleep disturbances, quality of life (QOL), and barriers to adherence to the medical prescription.

Patients' responses to the onset of ESRD and its continued treatment can alter their course, prognosis, and QOL. The psychological landscape shapes the patient's perception of his or her ability to cope with the diagnosis and the treatment's ongoing demands. Patients' state of mind, level of support, understanding of the disease, and adherence behaviors are all factors determining how patients adjust. Although the extent of one's physical illness affects one's psychosocial functioning, conversely, the strength of one's ability to cope can affect the course of medical illness. For example, increased depression and social strain can lead an ESRD patient to a cycle of decreased adherence, increased illness severity, and greater symptom burden.

Psychopathology

Depression

Depression is defined by the latest version of the *Diagnostic and Statistical Manual for Psychiatric Disorders* (*DSM-5*) as being present when an individual displays either a subjective depressed mood or a diminished interest or pleasure in activities, most of the day, nearly every day over a 2-week period, plus any four of the following additional symptoms: significant weight loss, insomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness or guilt, diminished ability to think or concentrate, or recurrent thoughts of death. These symptoms should cause impairment to the individual and be unrelated to a medication or medical condition. These last caveats could significantly complicate the diagnosis of depression in ESRD patients because they are typically treated with a variety of medications for kidney disease or other comorbid conditions that may have side effects that mimic depression. Furthermore, uremia and dialysis treatment itself can be the cause of somatic symptoms such as fatigue, insomnia, and inability to concentrate.

Despite the challenges in the accurate assessment of depression in patients treated with HD, a prevalence of depression of approximately 20% to 30% in HD patients has been reported when using rigorous clinician-administered diagnostic interviews. The rate is typically somewhat higher, toward 50%, if depressive effect is measured using a self-report measure.

Treatment

Despite these relatively high prevalence rates, depression may be undertreated in HD patients. There is also a paucity of studies evaluating depression treatment in HD patients. There are generally two approaches to treatment of depression in HD patients: pharmacologic and nonpharmacologic.

Pharmacologic Treatment

In an early study of a selective serotonin reuptake inhibitor (SSRI), 14 maintenance HD patients with major depression were randomly assigned to either treatment with fluoxetine or placebo. The antidepressant outperformed placebo at 4 weeks but not at 8 weeks. Improvement in depressive symptoms was reported in two observational studies of the effects of antidepressants in 136 peritoneal dialyses (PD) patients. These studies, however, had no control arm, had a small sample size, and had high medication discontinuation rates. Atalay et al. reported that treatment with sertraline (50 mg a day) for 12 weeks led to a decrease in depressive symptoms in 25 long-term PD patients. Similarly, this study did not have a control arm.

In a Korean study, paroxetine and individual supportive counseling were assessed in 34 depressed dialysis patients. There was a statistically significant but clinically mild response to the treatment. This study also suffered from a small sample size, lack of a placebo-control group, and absence of follow-up information.

A recent multisite study, the ASCEND trial, compared the efficacy of sertraline and cognitive-behavioral therapy (CBT) for depression in ESRD patients treated with maintenance HD. Both interventions proved to be efficacious and reduced depression scores. There was a slightly greater improvement in the medication group, but there was also a higher rate of minor side effects. The authors concluded that both treatments appear to be effective, and treatment recommendations should depend on risk profile, patient preference, and availability of resources.

Nonpharmacologic Treatment

Nonpharmacologic treatment interventions for depression in HD patients have been evaluated as well. Two primary interventions include CBT and exercise therapy.

Cognitive Behavioral Therapy. CBT is a type of psychotherapy that helps patients to dissect the relationships among their emotions, cognitions, and behaviors in order to identify and reframe irrational and self-defeating thoughts. These changes can improve their mood and, in turn, can empower people to control their unhelpful cognitive and behavioral patterns. CBT can be performed in groups or individually. CBT attempts to empower individuals to control their negative cognitive and behavioral patterns.

Three randomized controlled trials (RCTs) have rigorously examined CBT in patients treated with HD. Cukor et al. compared patients who received 10 CBT sessions administered chair side during regular HD treatments with a wait-list control group using a crossover design. CBT resulted in a significant reduction in depressive effect, increased perception of QOL, and better treatment adherence compared with control participants. In another RCT of 85 HD patients with major depressive disorder, CBT was compared with standard care. The CBT group demonstrated a more significant reduction in depressive effect than the standard care group, both at the end of treatment and at follow-up.

As before, in the ASCEND trial, chair-side CBT proved to be an efficacious treatment of depression. In this trial, participants received 10 sessions over 12 weeks of individual CBT, with significant reductions in clinician-administered and self-report measures of depression. CBT appears to be a promising intervention for reducing depression in ESRD patients treated with HD.

Exercise Therapy. The ability of exercise programs to improve mood in dialysis patients was recently tested in three small-scale studies. Across the studies, depression was statistically significant but modestly reduced in patients who engaged in physical activity. However, a limitation of these studies was low retention rates across the exercise programs, suggesting limited efficacy of this intervention as a broad-based strategy. Furthermore, these studies have not recruited formally diagnosed patients with depression into their studies but, instead, observed the effect of exercise on the full spectrum of mood scores.

Anxiety

The *DSM-5* classifies anxiety disorders by their common feelings of overwhelming fearfulness, dread, and uncertainty. Unlike relatively mild brief anxiety reactions, a true anxiety disorder must last at least 6 months. There was a significant change in the categorization of anxiety disorders with the recent update to DSM 5. Obsessive-compulsive disorders and posttraumatic stress disorders are no longer classified as anxiety disorders. Similar to depression, the assessment of anxiety is complicated by symptoms overlapping with uremia, multiple measurement tools, and imprecise definitions and cut-offs for clinical diagnosis.

Anxiety is a relatively common experience for HD patients. In studies, patients treated with HD exhibit significantly greater symptoms of anxiety compared with transplant patients and control participants. A systematic review of 55 studies of anxiety symptoms in ESRD patients indicated an overall prevalence rate of 38%, with levels of prevalence in individual studies ranging from 12% to 52%. Still, numerous studies have demonstrated that the role of anxiety in ESRD patients treated with HD remains underappreciated and understudied. It has also been suggested that anxiety contributes to dialysis nonadherence. A recent European study suggested that anxiety was associated with higher hospitalizations and mortality in dialysis patients. As of yet, there are no clinical trials testing the efficacy of anxiety treatments in ESRD populations. RCTs are certainly needed in this field because anxiety is associated with negative effects on general health, QOL, and a variety of psychosocial parameters in both ESRD patients and the general population. Only a well-designed RCT employing an effective intervention for anxiety in ESRD patients can determine if anxiety is causally related to poor outcomes in these patients.

Psychosocial Issues

Quality of Life

The demanding requirements of dialysis can have a significant and adverse effect on the overall QOL of dialysis patients. QOL has become more widely accepted as a salient health outcome and measure of treatment efficacy across medicine and in nephrology, specifically over the last two to three decades. Thus, preserving patients' QOL, or their sense of positive well-being, has become an essential component of medical treatment for ESRD.

Dialysis patients generally face poor health-related QOL (HRQOL). HRQOL involves the way patients manage their health in several domains (such as physical functioning, physical and emotional roles, social functioning, general health perception). Several studies have shown that patients undergoing dialysis are more likely to have compromised physical and emotional functioning compared to general populations. Decreased physical functioning of patients on HD has been associated with a higher risk of death. Increased physical activity in patients treated with HD has helped improve physical functioning and overall HRQOL and has been associated with other clinical benefits, including more positive affect, better sleep, and less pain.

Psychosocial variables are associated with variability within HRQOL. Depression, anxiety, social support, coping strategies, and health locus of control have all been linked to lower HRQOL in dialysis populations.

Social Support

Social support refers to the degree to which an individual belongs to a social network in which he or she gives and receives affection and aid, as well as an obligation to and from family members, friends, colleagues, community members, and medical personnel. Social support plays an integral role in health outcomes for ESRD patients through its influence on access to health care, treatment adherence, and psychological health. There is an interrelationship between social support and level of depressive symptoms, perception of illness effects, and overall satisfaction with life. Stronger social support is related to better health outcomes, dialysis adherence, and lower mortality for ESRD patients.

Sleep Disorders

Sleep disorders are more prevalent in ESRD patients than in the general population and are common in both HD and PD patients. The reason for higher rates of sleep-related issues and disorders in this population is likely multifactorial and due in part to the higher prevalence of restless legs syndrome (RLS), depression, pruritus, uremia, anemia, medications, sleep apnea, periodic limb movement, and metabolic changes in patients with ESRD. Walker et al. found that approximately 80% of ESRD patients receiving HD reported sleep complaints. Hui et al. found daytime sleepiness to be the most common sleep problem reported by Chinese PD patients. There is an association between sleep quality and lower QOL, health-related risks, and mortality in ESRD patients.

Insomnia

Symptoms of insomnia include difficulty with sleep initiation, sleep maintenance, or early-morning awakening that results in daytime impairment. Insomnia is often debilitating and occurs as a primary disorder or a comorbid disorder with other medical and/or psychiatric illnesses.

In the ESRD population, the prevalence of insomnia varies and may be as high as 69% compared with 10% in the general population. In the general population, insomnia is associated with lower HRQOL and impaired cognitive functioning. Severe insomnia has been associated with higher health care utilization, including medical provider visits, hospitalizations, and medication use.

Studies using polysomnographic data have demonstrated alterations in the sleep architecture of dialysis patients. Increased amounts of stage 1 and 2 sleep and decreased slow-wave and REM (rapid eye movement) sleep have been reported in HD patients. One study compared ESRD patients receiving HD with non-ESRD matched control participants. The ESRD sample had significantly lower sleep time and higher frequency of arousals compared with the control group. Parker et al. found that HD patients had shorter total sleep time, increased wake after sleep onset, lower sleep efficiency, higher periodic limb movement index, and longer latencies to sleep onset compared with a chronic kidney disease (CKD) group not undergoing dialysis.

Insomnia is generally thought of as having predominantly psychological as opposed to biologic etiologies. Therefore, the preferred treatments for insomnia are often behavioral and psychological, including sleep hygiene education (establishing a regular sleep schedule, decreasing caffeine intake, implementing regular physical activity, adjusting environmental factors) and CBT. Cognitive Behavioral Therapy—Insomnia (CBT-I) is an empirically validated psychotherapy tailored to the treatment of insomnia. In the general population, RCTs have found CBT to be an effective intervention. In an RCT of 24 PD patients, Chen et al. assessed a 4-week trial of CBT and sleep hygiene education versus sleep hygiene education only. Improvement in sleep latency, quality of sleep, daytime dysfunction, and fatigue were noted in the CBT group as measured by the Pittsburgh Sleep Quality Index and Fatigue Severity Scale. A larger-scale trial of CBT-I in patients with insomnia who are treated with HD (SLEEP-HD trial) is currently underway.

Pharmacologic treatment of insomnia includes benzodiazepines and other hypnotics. Given the risk of dependency, tolerance, sedation, withdrawal symptoms, and rebound symptoms, there is concern over their use. In a study of 195 HD patients, Yeh et al. found that benzodiazepines (42.6%) and hypnotics (20%) were the most frequently prescribed psychotropic drugs. However, Winkelmayer et al. found that benzodiazepines and zolpidem were associated with 15% higher mortality in 4024 dialysis patients. Dialysis patients with a diagnosis of chronic obstructive pulmonary disease were 50% more likely to use benzodiazepines or zolpidem and may be at a higher risk of mortality.

Restless Legs Syndrome and Periodic Limb Movement Disorder

The prevalence of RLS is about 30%–50% in patients with ESRD. RLS is a neurologic disorder characterized by unpleasant sensations, usually in the lower extremities, that involve a strong urge to move the legs. RLS symptoms often worsen during periods of inactivity and are temporarily relieved by movement. Symptoms frequently occur in the evening or night and interfere with sleep.

Treatment for RLS and periodic limb movement disorder (PLMD) in ESRD patients can include dopamine agonists such as L-dopa, and gabapentin, as well as behavioral modifications, such as addressing caffeine, alcohol, and nicotine intake and engaging in physical activity. Giannaki et al. randomized 24 HD patients with RLS into a progressive exercise training group (45 minutes of cycling during HD sessions, 3 days per week for 6 months with applied resistance) or a no-resistance exercise control group (45 minutes of cycling, 3 days per week for 6 months without resistance). RLS symptom severity significantly decreased in the resistance group compared with the control group. Improving iron deficiency has also been found to reduce RLS symptoms in ESRD patients.

Sleep Apnea

Sleep apnea syndrome (SAS) is characterized by disordered breathing during sleep. It is a common disorder in ESRD patients, with a reported prevalence of 50% to 70%. SAS is further classified as obstructive sleep apnea (OSA) (intermittent closure of the upper respiratory airway), central sleep apnea (CSA) (intermittent loss of respiratory drive), or mixed apneas, which is a combination of the two. Sleep apnea interferes with sleep initiation and sleep maintenance and can lead to daytime somnolence. The prevalence and severity of the disorder may worsen with the progressive decline in kidney function in CKD patients. Sleep apnea has been associated with higher rates of cardiovascular death in HD populations. The symptoms of sleep apnea may be difficult to detect in ESRD patients because common symptoms of uremia are fatigue, daytime somnolence, and cognitive dysfunction, which overlap with those of the sleep disorder.

Unruh et al. found that HD patients were four times more likely to have disordered breathing compared with control participants matched for age, gender, body mass index (BMI), and race after adjusting for cardiovascular disease and a history of diabetes. Risk factors for sleep apnea in the general population include age, gender, obesity, genetics, smoking status, craniofacial and upper airway abnormalities, neck girth, and central body fat distribution. In a study of 76 patients with OSA and ESRD and 380 patients with OSA and normal kidney function, gender and age were comparable; however, the ESRD group was generally not obese, and the mean BMI was lower compared to the control group. Also, in this study, the patients with ESRD were less likely to report symptoms, including snoring, apnea during sleep, nonrefreshing sleep, and morning headaches. The ESRD patients had lower snoring intensity compared with the control group, confirmed by polysomnography.

Treatment of sleep apnea includes addressing underlying medical conditions and using continuous positive airway pressure (CPAP) breathing. Nocturnal HD improves sleep apnea in ESRD patients. Hanly et al. assessed 14 HD patients who were switched from conventional HD (4-hour sessions 3 days per week) to nocturnal HD (8 hours, six or seven nights per week) and found a reduction in the frequency of apneas and hypopneas. The apnea-hypopnea index on nights participants were not receiving nocturnal HD was higher than nights when they were undergoing treatment, although it was still lower than when they were receiving conventional HD. Tang et al. demonstrated improvement in sleep apnea in patients treated with nocturnal PD compared with those treated with continuous ambulatory PD (CAPD). They attributed this to improved fluid control during sleep. Interestingly, in the Frequent Hemodialysis Network (FHN) trial, neither frequent in-center HD nor home nocturnal HD demonstrated significant improvements in self-reported sleep quality compared with conventional HD at 12 months.

Adherence

The most common definition of adherence is "the extent to which a person's behaviors in taking medications, following a diet, and/or executing lifestyle changes corresponds with agreed-upon recommendations from a healthcare provider." Patients treated with HD are asked to attend a dialysis regimen of 4-hour treatments 3 times a week, have a high pill burden, and complex dietary restrictions that include fluid, phosphate, and sodium. Adherence to the medical regimen is an important determinant of outcome in HD patients, although accurate measurement of adherence is challenging. Assessment tools and indices are often not true measures of adherence but rather are health indicators (e.g., serum phosphate, sodium, blood urea nitrogen [BUN], and potassium concentrations and interdialytic weight gain [IDWG]) that can serve as proxy markers for adherence.

Types of Nonadherence

Nonadherence can be inadvertent (i.e., because of lack of understanding, forgetfulness, or miscommunication with health care professionals) or attentional (i.e., when patients actively choose not to follow their regimen). In this chapter, we examine nonadherence in the HD treatment prescription, fluid and dietary restrictions, and medication prescription.

Hemodialysis Treatment Prescription Nonadherence

Dialysis prescription nonadherence is measured by objective (i.e., the number of skipped dialysis sessions or the number of shortened sessions) and subjective measures (i.e., staff assessment and patient report). There are no standardized measurements that define nonadherence to the HD treatment prescription. For example, skipping one or more dialysis sessions per month has been used by some to define nonadherence, but others have used a higher cut-off.

In the United States, approximately 50% of HD patients do not adhere to their prescribed treatment regimen, and while life changes for HD patients are extensive, adherence to this multifaceted regimen may minimize the likelihood of adverse medical outcomes. Among 182,536 dialysis patients, Chan et al. found that patients who missed their scheduled dialysis treatments were more likely to be hospitalized. Gray, Cohen, and Brunelli looked at 4,656,477 scheduled HD treatments over 1 year at a large dialysis organization. They found that 9.9% of treatments were missed and that a single missed treatment was associated with a 1.4-fold greater risk of hospitalization and a 2.18-fold greater risk of death in the subsequent 30 days. Similarly, the Dialysis Outcomes and Practice Patterns Study (DOPPS) looked at 8501 patients treated with HD in 20 countries and found that in those countries with a 4-month missed treatment risk $>5\%$, HD patients were more likely to be hospitalized and die if they missed one or more treatments

over a 4-month period. Nonadherence ranged from < 1% in Italy and Japan to 24% in the United States. The authors noted that this variability suggests that the nonadherence behavior may be modifiable, influenced by cultural norms and health care delivery models.

Fluid and Dietary Nonadherence

Fluid and dietary nonadherence may be measured by biochemical indices, including serum potassium concentration, phosphate levels, BUN, and IDWG. While there are no standard cut-off levels for potassium and phosphate that define nonadherence, studies have used a range from 5.5 to 8 mEq/L as a marker of potassium nonadherence and a range from 5.5 mg/dL to 7.5 mg/dL as a marker of phosphate nonadherence. These measurements are confounded and may not solely reflect dietary factors since hormonal influences, such as insulin secretion and resistance, as well as parathyroid hormone release and action, may affect circulating potassium and phosphate concentrations in dialysis patients with residual kidney function. Dialysis patients also may often have difficulty understanding, assimilating, and following dietary recommendations. Although a typical diet provides approximately 1500 mg of phosphate per day (from milk, meat, poultry, fish, cereal, and eggs), the recommended dietary allowance of phosphate intake for dialysis patients is 700 mg/day. Cupisti et al. showed that a dietary intervention and counseling effectively helped HD patients decrease phosphate and calcium intake. Similarly, Ford et al. showed significant improvement in patients' phosphate levels after 6 months when patients were given a 20- to 30-minute diet education program each month. Sullivan et al. showed a decline in serum phosphate levels in the intervention group (i.e., those who received a dietary education intervention vs. the control group) after 3 months. Another study found that an educational program for adherence to dietary restrictions was more effective in lowering phosphate levels in the long term compared with monthly nutrition counseling and information regarding the use of phosphate binders. Fissell et al. looked at data collected from 5262 HD patients across 12 countries in the DOPPS. They found an association between greater phosphate binder pill burden and phosphate binder nonadherence, which was associated with higher serum phosphate and intact parathyroid hormone concentrations. Nonadherence ranged from 33% in Belgium to 57% in the United States. The authors suggested a simplified phosphate binder regimen could lead to increased adherence. Schlatter and Ferrans found that an educational intervention in a group of 29 HD patients with high phosphate levels had no effect on serum phosphate levels despite an increase in knowledge about phosphate.

IDWG has been measured with both absolute and relative values and is a marker of increased sodium and fluid intake. In the United States, some studies suggest that 10% to 20% of HD patients routinely exhibit high IDWGs, which has been associated with lowered effectiveness of dialysis, hypertension, congestive heart failure, pulmonary edema, and death. Smith et al. explored potential barriers and facilitators to fluid adherence in dialysis patients. They found that knowledge and accurate self-assessment of health were associated with increased adherence. The most common barrier was an overall lack of motivation to restrict fluid intake. Social support was sometimes a facilitator and sometimes a barrier, depending on the extent to which family members and friends engaged in the patient's treatment and guided and encouraged them to make necessary lifestyle changes.

In the Hemodialysis Self-management Intervention Randomized Trial (HED-SMART), Griva et al. evaluated 235 HD patients who were randomized to usual care or a self-management training program. They found lower IDWG in the intervention group and not in the control group, where it worsened significantly at 3-month assessment.

In a study that targeted depression symptoms, patients exhibited a decrease in IDWG when their mood improved. While participants were in the active phase of treatment, their IDWG rates fell within the target range. Unfortunately, the adherence behaviors did not continue through the 3-month follow-up, with mean levels of adherence returning to baseline levels, despite mood symptoms remaining low.

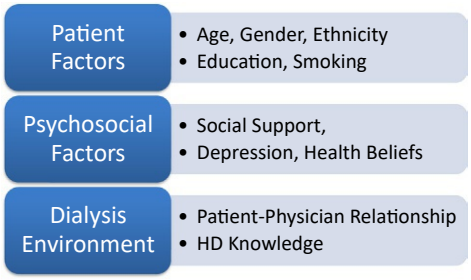
Medication Prescription Nonadherence

Medication prescription nonadherence in dialysis patients can be measured by both objective and subjective means. Objective measures include monitoring, remote electronic monitoring, and pill counts. Subjective measures include questionnaires completed by the health care provider or completed by the patient.

The prevalence of nonadherence to medication ranges from 21% to 74% in ESRD patients, depending on the type of assessment. Several investigators have explored the barriers to medication adherence in dialysis patients. Feelings of discomfort, forgetfulness, use of multiple medications (since patients are generally prescribed an average of 10–12 medications per day), fear of drug interactions, medical expenses, lack of knowledge, and poor communication with physicians are barriers to adherence.

Factors Affecting Hemodialysis Nonadherence

The life changes demanded of the HD patient are extensive, and nonadherence to the dialysis prescription and other medical requirements is common, with estimates for nonadherence to aspects of the HD prescription ranging from 22% to 86%, depending on the definition and measurement of adherence. In trying to understand what drives nonadherence, many factors have been evaluated for their possible contribution in patients treated with HD. These factors include patient characteristics, psychosocial influences, and elements of the dialysis environment (Fig. 55.1).



• **Fig. 55.1** Factors possibly contributing to nonadherence in patients with end-stage renal disease treated with hemodialysis *(HD)*.

Patient Characteristics and Nonadherence

Studies have evaluated the influence of age, gender, ethnicity, smoking, and education on adherence behaviors in HD. Across studies, and regardless of the type of recommended treatment, younger patients are more likely to be nonadherent than older patients. Smokers and patients with lower levels of education are also more likely to be nonadherent. Findings regarding gender have been mixed, although most studies find men more likely to be nonadherent than women. One study that included HD patients from the United States, Japan, and Europe found that women were more likely to be nonadherent to dietary recommendations. Similarly, ethnic differences in adherence behaviors have been mixed. Leggat et al. looked at 6251 HD patients in the U.S. Renal Data System and found black patients to be more nonadherent to the dialysis regimen (i.e., more likely to skip treatments), but some other studies found no race differences.

Psychosocial Factors and Nonadherence

The relationships between psychosocial factors and adherence have been examined. In the majority of studies, some, including the patient-physician relationship and depression, have been found to consistently be associated with adherence, while others, including health literacy, show conflicting results.

Social support may be a source of positive impact on adherence in HD patients. The influence of perceived social and family support is generally associated with better adherence behaviors in patients being treated with HD, but results have been mixed. Several studies found a significant association between social support and adherence to recommended fluid intake, such that those with lower levels of social support were less likely to adhere to dietary recommendations. Christensen et al. found a positive relationship between social support and adherence to the dialysis treatment, such as higher levels of perceived support were associated with enhanced adherence to the dialysis treatment prescription. Three other studies found a strong association between lower levels of social support and a greater likelihood of medication nonadherence. In contrast, two other studies did not find such a relationship. Smith et al. found that social support was sometimes a facilitator and sometimes a barrier, depending on the extent to which family members and friends engaged in the patient's treatment and guided and encouraged them to make the necessary lifestyle changes. Finally, another study found that social support had no influence on adherence.

Health beliefs, particularly feelings of self-efficacy, relate to an individual's perceived ability to perform a certain behavior. These perceptions of self-efficacy may influence whether individuals will attempt certain behaviors and how the behaviors will be carried out.

Patients treated with dialysis who have lower self-efficacy beliefs have been found to be less adherent to treatment than HD patients with higher self-efficacy beliefs. Two studies found that patients with lower dietary self-efficacy had higher potassium levels and IDWG. There is also evidence that increasing self-efficacy can lead to improved adherence. An RCT showed that patients who received self-efficacy enhancement training had a greater reduction in IDWG compared to a control group. In the HED-SMART, an intervention designed to promote feelings of greater self-efficacy through a self-management training program showed a reduction in IDWG in the intervention group and not in the control group.

Several studies have shown that depression predicts lower adherence in dialysis patients. Khalil et al. suggested that depressed patients feel hopeless and have a negative self-image and outlook, which in turn manifests as an inability to adhere to treatment. Cukor et al. found that depressive affect is strongly related to medication adherence in the ESRD population.

Illness perceptions refer to the patients' appraisals of how their disease affects their everyday physical and emotional functioning and overall QOL. Treatment perceptions refer to patients' beliefs about medication. Various studies have found that patients with more optimistic illness perceptions and positive perceptions about the benefits of medication are more likely to be adherent.

Elements of the Dialysis Environment and Nonadherence

Trust is an essential quality between the physician and patient and may be related to patients' treatment adherence behaviors. Allowing open communication between patients and their health care providers and allowing patients to participate in decision making have been shown to enhance adherence. One preliminary study found that higher patient satisfaction with physicians was associated with better attendance and greater adherence to the treatment. Additionally, frequent patient-physician contact may lead to better adherence in dialysis patients. Plantinga et al. found that HD patients who attended clinics with limited patient-physician contact were less satisfied with their care and more likely to be nonadherent to all aspects of their treatment.

Health literacy is defined as the "ability to obtain, process, and understand basic health information in order to make appropriate health decisions about one's health and medical care." Low health literacy has been linked

to health disparities in various populations and health complications, including diabetes and death in ESRD. It correlates with lower QOL and may influence adherence behaviors, particularly taking prescribed medications, following dietary and fluid recommendations, and attending dialysis appointments. Smith et al. explored potential barriers and facilitators to fluid adherence in dialysis patients. They found that knowledge and accurate self-assessment of health were associated with better adherence. Tohme et al. studied 286 HD patients over 24 months and found that low health literacy was associated with nonadherence to the dialysis prescription. Green et al. found that patients with low health literacy were also more likely to be nonadherent to the dialysis prescription, having more missed dialysis appointments.

There are several possible mechanisms through which health literacy may affect adherence. Patients with low health literacy may have low reading comprehension skills or knowledge of their disease that prevents them from fully understanding self-care demands and the medical, diet, fluid, and dialytic prescriptions. Limited patient knowledge may also affect patients' self-efficacy and their confidence that they can be adherent. Nonadherence is associated with higher risk for complications proving that health literacy may be an important factor in the care of patients with kidney disease.

The impact of HD-related knowledge on adherence behaviors in HD patients has been examined in a number of studies, and the findings are inconsistent. Some studies demonstrate that patients with more knowledge about their disease are more likely to adhere to their treatment regimens, while others' findings do not support this. For example, one intervention study that investigated the change in patients' adherence behavior to taking phosphate binders after they were provided with increased knowledge about the binders (compared with those who did not receive phosphate education) found that patients who received the educational intervention had increased adherence rates, from 82.5% in week 1 to 94% at week 13, compared with the adherence rate change from 85.5% at week 1 to 75.9% at week 13 in the control patients. Another intervention study in which patients were given structured educational sessions showed a decrease in IDWG from 2.64 kg to 2.21 kg. In their study, Casey et al. found that patient education regarding fluid management improved adherence in 48% of the sample group. In another study, patients who received HD-related knowledge had better fluid adherence than those who did not receive the education. In contrast, Tanner et al., Cummings et al., Long et al., and Wells et al. found no association between more HD-related knowledge and adherence behaviors.

Addressing Hemodialysis Nonadherence

Given the high rates of nonadherence in HD patients, effective treatment options to improve adherence have been evaluated. Interventions include an array of educational, biopsychosocial, and behavioral designs to help HD patients as they experience multiple and necessary lifestyle changes. Effects of the interventions have been mixed, and disparate results are likely due to differences in sample size, patient characteristics, and adherence outcomes assessed in the studies. As study in this area grows, focusing on reducing these deficits is necessary.

Some educational interventions have proved effective for fluid adherence, but others have not. Cupisti et al. showed that a dietary intervention and counseling effectively helped HD patients decrease phosphate and calcium intakes. Similarly, Ford et al. showed significant improvement in patients' phosphate levels after 6 months when patients were given a 20- to 30-minute diet education program each month. Sullivan et al. showed a decline in serum phosphate levels in the intervention group (i.e., those who received a dietary education intervention vs. the control group) after 3 months. Another study found that an educational program for adherence to dietary restrictions was more effective in lowering phosphate levels in the long term compared with monthly nutrition counseling and information regarding the use of phosphate binders.

However, Schlatter and Ferrans found that a teaching intervention in a group of 29 HD patients with high phosphate levels had no effect on serum phosphate levels despite an increase in phosphate knowledge. Likewise, Long et al. and Wells et al. found that an educational program increased knowledge but did not improve dialysis patients' adherence. One study that targeted depression symptoms had an effect on IDWG. Although participants were in the active phase of treatment, their IDWGs rates fell to within the target range. However, the adherence behaviors did not continue through the 3-month follow-up, with mean levels of adherence returning to baseline levels.

Thus, knowledge and education alone do not consistently increase adherence. It is possible that tailoring the intervention to the needs and characteristics of individual patients may be more beneficial.

One strategy for improving medication adherence in dialysis patients is to simplify drug regimens. This can be done by either using fixed-dose combinations to allow for once-daily dosing, using drugs that are administered less often, administering the drugs intravenously at the end of the dialysis session, or orally under direct supervision. Such strategies may often be incompatible with clinical requirements for drug administration, insurance issues, or clinic policies.

Another proposed strategy is to include a multidisciplinary approach in which all members of the treatment team (i.e., the patient, nursing and technical staff, administrators, and physician) are engaged and in open communication in order to reduce barriers, include the patient in the decision-making process, and enhance adherence. However, caution is warranted because the success of such approaches has not been demonstrated thus far to improve adherence in the HD population.

Conclusion

HD, although lifesaving, is a taxing, demanding, and often lifelong treatment. Patients' psychological resilience and available resources are associated with their QOL, psychological health, adherence to treatment demands, and even symptom burden and survival. Psychosocial factors interact in a complex fashion and may influence adherence with the dialysis prescription. Depression, for example, is a risk factor for nonadherence and poor outcomes. Successful treatment of depression using pharmacologic and nonpharmacologic therapies certainly can improve mood but may also improve adherence and QOL, which may, in turn, decrease hospitalizations and death. As physicians' treatment goals increasingly embrace a biopsychosocial perspective, more clinical and scientific attention is required to understand the factors that predict mental health, QOL, and treatment compliance in dialysis patients.

The study of the impact of the psychosocial functioning of ESRD patients is still in the early stages of development. However, it is clear that the psychosocial status of the ESRD patient can have a meaningful impact on the disease course. There needs to be rigorous inquiry about the strategies that can optimize psychosocial functioning and medical outcomes in patients with ESRD treated with dialysis.

Recommended Reading

Al Salmi I, Larkina M, Wang M, et al. Missed hemodialysis treatments: international variation, predictors, and outcomes in the Dialysis Outcomes and Practice Patterns Study (DOPPS).

American Journal of Kidney Diseases. 2018;72(5):634–643. *Large-scale study linking missed dialysis sessions with negative health outcomes.*

Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Association; 2013.

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders defines and explains all current psychiatric diagnoses.

Casey J, Johnson V, McClelland P. Impact of stepped verbal and written reinforcement of fluid balance advice within an outpatient hemodialysis unit: a pilot study. *J Hum Nutr Diet.* 2002;15(1):43–47.

This study reported that patient education regarding fluid management improved adherence in 48% of the target group.

Chan KE, Thadhani RI, Maddux FW. Adherence barriers to chronic dialysis in the United States. *J Am Soc Nephrol.* 2014;25:2642–2648.

Large data set highlighting the negative consequences of dialysis nonadherence.

Chen HY, Chiang CK, Wang HH, et al. Cognitive-behavioral therapy for sleep disturbance in patients undergoing peritoneal dialysis: a pilot randomized controlled trial. *Am J Kidney Dis.* 2008;52(2):314–323.

A pilot trial of CBT for insomnia techniques for patients treated with PD.

Cohen SD, Norris L, Acquaviva K, Peterson RA, Kimmel PL. Screening, diagnosis, and treatment of depression in patients with end-stage renal disease. *Clin J Am Soc Nephrol.* 2007;2(6):1332–1342.

A general review of assessment and treatment of depression in ESRD patients.

Cohen SD, Sharma T, Acquaviva K, et al. Social support and chronic kidney disease: an update. *Adv Chronic Kidney Dis.* 2007;14(4):335–344.

A review of the role of social support in CKD.

Cooper-Patrick L, Gallo JJ, Gonzales JJ, et al. Race, gender, and partnership in the patient-physician relationship. *JAMA.* 1999;282(6):583–589.

Highlights the significance of trust between patients and providers.

Cukor D, Cohen SD, Peterson RA, Kimmel PL. Psychosocial aspects of chronic disease: ESRD as a paradigmatic illness. *J Am Soc Nephrol.* 2007;18:3042–3055.

A review of the key theoretical constructs and the role of psychosocial factors in relationship to outcomes in dialysis patients using ESRD as a key example of chronic illness.

Cukor D, Coplan J, Brown C, et al. Depression and anxiety in urban hemodialysis patients. *Clin J Am Soc Nephrol.* 2007;2:484–490.

Single-site study reporting the prevalence of psychiatric disorders and interrelationship of anxiety and depression in an HD unit using a clinician-administered instrument.

Cukor D, Coplan J, Brown C, et al. Anxiety disorders in adults treated by hemodialysis: a single-center study. *Am J Kidney Dis.* 2008;52:128–136.

Single-site study of prevalence of anxiety symptoms and disorders in an HD center.

Cukor D, Ver Halen N, Asher DR, et al. Psychosocial intervention improves depression, quality of life, and fluid adherence in hemodialysis. *J Am Soc Nephrol.* 2014;25:196–206.

Multi-site RCT examining chairside CBT in dialysis units. Demonstrated substantial improvements in mood, QOL, and interdialytic weight gain.

Cupisti A, D'Alessandro C, Baldi R, Barsotti G. Dietary habits and counseling focused on phosphate intake in hemodialysis patients with hyperphosphatemia. *J Ren Nutr.* 2004;14(4):220–225.

Demonstrated that a targeted educational intervention was successful at improving dietary compliance.

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An RCT testing exercise as an intervention for RLS.

Green JA, Mor MK, Shields AM, Sevick MA, Arnold RM, Palevsky PM, et al. Associations of health literacy with dialysis adherence and health resource utilization in patients receiving maintenance hemodialysis. *Am J Kidney Dis.* 2013;62(1):73–80.

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Gray KS, Cohen DE, Brunelli SM. In-center hemodialysis absenteeism: prevalence and association with outcomes. *CEOR.* 2017;9:307.

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Griva K, Nandakumar M, Jo-an HN, Lam KF, McBain H, Newman SP. Hemodialysis self-management intervention randomized trial (HED-SMART): a practical low-intensity intervention to improve adherence and clinical markers in patients receiving hemodialysis. *American Journal of Kidney Diseases.* 2018;71(3):371–381.

Demonstrated decreased IDWG in a group treated with self-management intervention.

Hanly P, Pierratos A. Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis. *N Engl J Med.* 2001;344(2):102–107.

Demonstrated improvement in OSA symptoms in HD patients who switched to nocturnal HD.

Hedayati S, Bosworth H, Briley L, et al. Death or hospitalization of patients on chronic hemodialysis is associated with a physician-based diagnosis of depression. *Kidney Int.* 2008;74:930–936.

Examined the rates of death or hospitalization of dialysis patients after a depression diagnosis. Depression was associated with increased rates of both outcomes.

Hedayati SS, Finkelstein FO. Epidemiology, diagnosis and management of depression in patients with CKD. *Am J Kidney Dis.* 2009;54:741–752.

Reviews diagnostic and therapeutic issues in the management of depression in ESRD patients.

Kaveh K, Kimmel PL. Compliance in hemodialysis patients: multidimensional measures in search of a gold standard. *Am J Kidney Dis.* 2001;37(2):244–266.

Reviews compliance measures and associations of compliance with outcomes in HD patients.

Khalil AA, Frazier SK. Depressive symptoms and dietary nonadherence in patients with end-stage renal disease receiving hemodialysis: a review of quantitative evidence. *Issues Ment Health Nurs.* 2010;31(5):324–330.

Develops a theoretical model between depression and nonadherence for ESRD patients.

Kimmel PL. Just whose quality of life is it anyway? Controversies and consistencies in measurements of quality of life. *Kidney Int.* 2000;57:S113–S120.

A general review of assessment of quality of life in HD patients and the relationship of selected measures to outcomes.

Kimmel PL. Psychosocial factors in dialysis patients. *Kidney Int.* 2001;59:1599–1613.

A general review of psychosocial factors and their importance for dialysis patients.

Kimmel PL, Peterson RA. Depression in end-stage renal disease patients treated with hemodialysis: tools, correlates, outcomes, and needs. *Semin Dial.* 2005;18:91–97.

A review of the literature of depression in ESRD patients. Focuses on the known associations and highlights future research directions.

Kimmel PL, Peterson RA, Weihs KL, et al. Aspects of quality of life in hemodialysis patients. *J Am Soc Nephrol.* 1995;6(5):1418–1426.

Reviews the construct of QOL and how it can be applied to HD populations.

Kimmel PL, Peterson RA, Weihs KL, et al. Behavioral compliance with dialysis prescription in hemodialysis patients. *J Am Soc Nephrol.* 1995;5:1826–1834.

Demonstrates the association of behavioral compliance in dialysis patients (shortening and skipping behaviors) to poorer outcomes.

Kimmel PL, Peterson RA, Weihs KL, et al. Multiple measurements of depression predict mortality in a longitudinal study of chronic hemodialysis outpatients. *Kidney Int.* 2000;*57*(5):2093–2098.

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Koo JR, Yoon JY, Joo MH, et al. Treatment of depression and effect of antidepression treatment on nutritional status in chronic hemodialysis patients. *Am J Med Sci.* 2005;329:1–5.

Single-site study found improvement in mood and nutritional status with the successful treatment of depression.

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Lopes AA, Bragg-Gresham JL, Satayathum S, McCullough K, Pifer T, Goodkin DA, et al. Worldwide Dialysis Outcomes and Practice Patterns Study Committee: Health-related quality of life and associated outcomes among hemodialysis patients of different ethnicities in the United States: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis.* 2003;41(3):605–615.

Key paper demonstrates an association between widely used HRQOL measures and mortality in U.S. HD patients.

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This study demonstrates an association between social support and mortality in U.S. HD patients.

Mehrotra R, Cukor D, Unruh M, et al. Comparative efficacy of therapies for treatment of depression for patients undergoing maintenance hemodialysis: a randomized clinical trial. *Annals of Internal Medicine.* 2019;*170*(6):369–379.

Large-scale RCT highlighting the comparative efficacy of sertraline and cognitive behavioral therapy for depression in patients with ESRD treated with HD.

Merlino G, Piani A, Dolso P, et al. Sleep disorders in patients with end-stage renal disease undergoing dialysis therapy. *Nephrol Dial Transplant.* 2006;21(1):184–190.

Reports rates of sleep disturbance and sleep diagnosis in the HD population.

Novak M, Shapiro CM, Mendelssohn D, Mucsi I. Reviews: diagnosis and management of insomnia in dialysis patients. *Semin Dial.* 2006;19(1):25–31.

Thorough review paper examining the causes, epidemiology, and treatment of insomnia in HD populations.

Parker KP, Bliwise DL, Bailey JL, Rye DB. Polysomnographic measures of nocturnal sleep in patients on chronic, intermittent daytime haemodialysis vs those with chronic kidney disease. *Nephrol Dial Transplant.* 2005;20:1422–1428.

Compared CKD patients treated with HD with those not requiring HD on subjective and objective sleep quality measures.

Plantinga LC, Fink NE, Sadler JH, Levey AS, Levin NW, Rubin HR, et al. Frequency of patient–physician contact and patient outcomes in hemodialysis care. *J Am Soc Nephrol.* 2004;15(1):210–218.

Demonstrated that HD patients who attended clinics with limited patient–physician contact were less satisfied with their care and more likely to be nonadherent.

Schouten RW, Haverkamp GL, Loosman WL, et al. Anxiety symptoms, mortality, and hospitalization in patients receiving maintenance dialysis: a cohort study. *Am J Kidney Dis.* 2019;74(2):158–166.

Found an association between higher anxiety levels and increased hospitalizations.

Schlatter S, Ferrans CE. Teaching program effects on high phosphorus levels in patients receiving hemodialysis. *ANNA J.* 1998;25(1):31–36.

Found that an educational intervention in a small group of HD patients with high phosphate levels had no effect on serum phosphate levels despite an increase in knowledge.

Smith K, Coston M, Glock K, et al. Patient perspectives on fluid management in chronic hemodialysis. *J Ren Nutr.* 2010;20(5):334–341.

Conducted interviews with HD patients to determine the most salient factors associated with fluid compliance. Lack of patient motivation was the key barrier.

Tang SCW, Lam B, Ku PP, et al. Alleviation of sleep apnea in patients with chronic renal failure by nocturnal cycler–assisted peritoneal dialysis compared with conventional continuous ambulatory peritoneal dialysis. *J Am Soc Nephrol.* 2006;17:2607–2616.

Trial showing improvement in sleep apnea scores in patients treated with nocturnal peritoneal dialysis.

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Used polysomnography to compare HD patients with patients from the Sleep Heart Health Study and found higher rates of OSA in HD.

Walker S, Fine A, Kryger MH. Sleep complaints are common in a dialysis unit. *Am J Kidney Dis.* 1995;26(5):751–756.

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Winkelmayer WC, Mehta J, Wang PS. Benzodiazepine use and mortality of incident dialysis patients in the United States. *Kidney Int.* 2007;72:1388–1393.

Observational study using administrative data reported rates of all-cause mortality associated with benzodiazepine use in U.S. ESRD patients.

Wuerth D, Finkelstein SH, Ciarcia J, et al. Identification and treatment of depression in a cohort of patients maintained on chronic peritoneal dialysis. *Am J Kidney Dis.* 2001;37(5):1011–1017.

Study of SSRI treatment of depression in PD patients. Small-scale study with methodological challenges.

Yeh CY, Chen CK, Hsu HJ, et al. Prescription of psychotropic drugs in patients with chronic renal failure on hemodialysis. *Ren Fail.* 2014;36(10):1545–1549.

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56

Evaluation and Treatment of Sexual Dysfunction

BIFF F. PALMER, MD

Introduction

Sexual dysfunction is a common finding in both men and women with chronic kidney disease. Common disturbances include erectile dysfunction in men, menstrual abnormalities in women, and decreased libido and fertility in both sexes. These abnormalities are primarily organic in nature and are related to uremia as well as the other comorbid conditions that frequently occur in the chronic kidney disease patient. Fatigue and psychosocial factors related to the presence of chronic disease are also contributory factors.

Sexual Dysfunction in Uremic Men

Erectile dysfunction is one of the most common manifestations of sexual dysfunction in men with chronic kidney disease. The prevalence of this disorder has been reported to be as high as 70%–80% and is similar between patients on hemodialysis and patients on peritoneal dialysis. In addition to abnormalities in blood flow and neural input to the penis, abnormalities in the pituitary-gonadal axis play a prominent role in the genesis of this disorder.

Chronic kidney disease is associated with impaired spermatogenesis and testicular damage, often leading to infertility. Semen analysis typically shows decreased volume of ejaculate, either low or complete azoospermia, and a low percentage of sperm motility. Histologic findings include damage to the seminiferous tubules and interstitial fibrosis, and calcifications in the epididymis and corpora cavernosa. The factors responsible for testicular damage in uremia are not well understood, but chronic exposure to phthalates in dialysis tubing may play a role.

The endocrine function of the testes is also abnormal in chronic kidney disease (Table 56.1). Total and free testosterone levels are typically reduced, although the binding capacity and concentration of sex hormone-binding globulin are normal. Low testosterone levels lead to increased plasma concentration of the pituitary gonadotropin, luteinizing hormone (LH) since testosterone normally inhibits LH release through a negative feedback loop. Low serum testosterone levels are associated with increased mortality in dialysis patients. Follicle-stimulating hormone (FSH) secretion is also increased in men with chronic kidney disease, although to a more variable degree such that the LH/FSH ratio is typically increased. FSH release by the pituitary normally responds to feedback inhibition by a peptide product of the Sertoli cells called inhibin. The plasma FSH concentration tends to be highest in those uremic patients with the most severe damage to the seminiferous tubules and presumably the lowest levels of inhibin. Increased FSH levels may be a predictor of incomplete recovery of spermatogenic function following kidney transplantation. Elevated plasma prolactin levels are commonly found in dialyzed men primarily due to increased production and, to a lesser extent, reduced metabolic clearance. Both increased parathyroid hormone and zinc deficiency may play a role in the increased levels.

Gynecomastia occurs in approximately 30% of men on maintenance hemodialysis. This disorder most often develops during the initial months of dialysis and then tends to regress as dialysis continues. The pathogenesis of gynecomastia is unclear. Although elevated prolactin levels and an increased estrogen-to-androgen ratio seem attractive possibilities, most data fail to support a primary role for abnormal hormonal function. Alternatively, a mechanism similar to that responsible for gynecomastia following refeeding of malnourished patients may be involved.

Evaluation of Sexual Dysfunction in Uremic Men

Disturbances in the hypothalamic-pituitary-gonadal axis, abnormalities in the sympathetic nervous system, and derangements in the arterial supply or venous drainage of the penis all need to be considered when evaluating and ultimately treating the impotent chronic kidney disease patient. In addition, the psychological effects of chronic illness and lifestyle limitations may negatively impact sexual function.

TABLE 56.1 Factors Involved in the Pathogenesis of Impotence in Uremic Men

- Vascular system
  - Occlusive arterial disease
  - Veno-occlusive disease and venous leakage
- Neurologic system
  - Impaired autonomic function due to uremia and comorbid conditions
- Endocrine system
  - Gonadal function
    - Decreased production of testosterone
  - Hypothalamic–pituitary function
    - Blunted increase in serum LH levels
    - Decreased amplitude of LH secretory burst
    - Variable increase in serum FSH levels
    - Increased prolactin levels
- Psychological system
- Other factors
  - Zinc deficiency
  - Medications
  - Anemia
  - Secondary hyperparathyroidism

FSH, Follicle-stimulating hormone; *LH*, luteinizing hormone.

A thorough history and physical examination can provide useful information during the initial evaluation of a patient with impotence. A history of normal erectile function prior to the development of kidney failure is suggestive of a secondary cause of impotence. Symptoms or physical findings of neuropathy, as in a patient with a neurogenic bladder, would be particularly suggestive of a neurologic etiology. Similarly, symptoms or signs of peripheral vascular disease may be a clue to the presence of a vascular obstruction to penile blood flow. The lack of secondary sexual characteristics, such as facial, axillary, and pubic hair, and the presence of small soft testicles suggest primary or secondary hypogonadism as the cause of the impotence. Neurogenic and vascular causes are more likely to be associated with normal-sized testicles. Even when the history and physical examination point to a specific abnormality, further evaluation may be warranted since erectile dysfunction is multifactorial in these patients.

A review of the patient's medications may reveal a drug that could be potentially playing a role in impairing sexual function. Antihypertensive medications are common offenders, with centrally acting agents and beta-blockers being the most commonly implicated agents in causing impotence. The angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are associated with a lower incidence of impotence and represent a useful alternative in chronic kidney disease patients with hypertension. Other drugs commonly implicated include cimetidine, phenothiazines, tricyclic antidepressants, selective serotonin reuptake inhibitors, and metoclopramide.

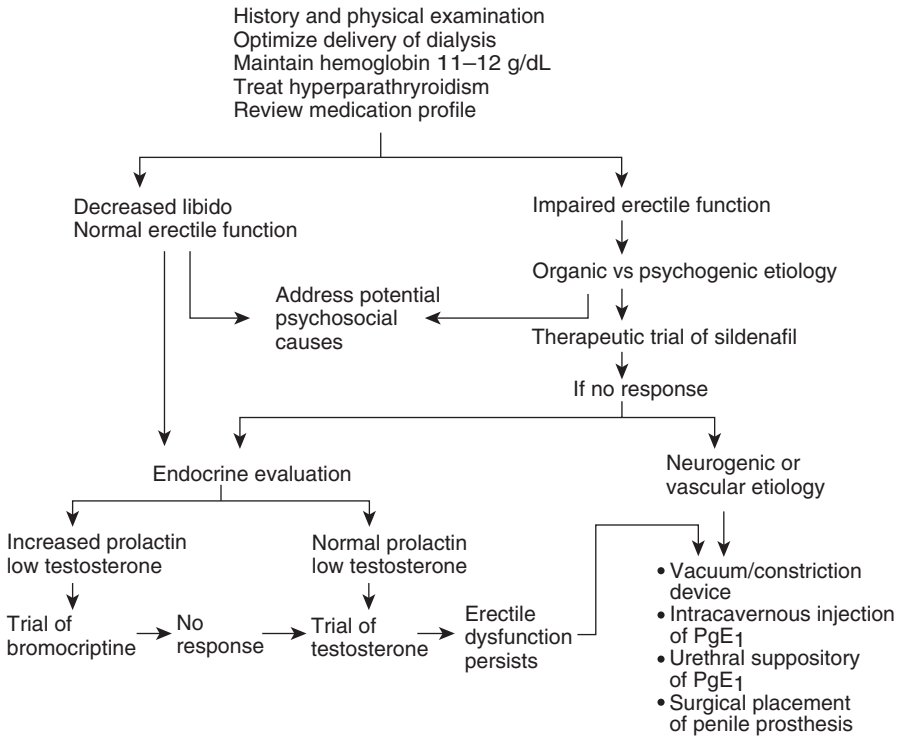
If the history and physical examination revealed no obvious cause, then a psychological cause of erectile dysfunction should be considered. Testing for the presence of nocturnal penile tumescence (NPT) has been used in some centers as a means to discriminate between a psychological and organic cause of impotence. The basis for this test is that during the rapid eye movement stage of sleep, males normally have an erection. The assumption is that men with a psychological cause of impotence would still experience erections while asleep, whereas the absence of an adequate erection would make an organic cause more likely. If a patient is found to have nocturnal erections, then psychological testing and evaluation are indicated. NPT testing is not infallible, and if a patient has a normal test and no psychological cause is found, then evaluation for an organic cause should still be pursued.

There are tests that may aid the discrimination between a neurogenic and vascular cause of impotence. Tests used to exclude a vascular etiology of impotence include Doppler studies to measure penile blood flow, penile blood pressure, and penile pulse palpation. Neurogenic impotence is suggested by detecting a prolonged latency time of the bulbocavernous reflex or confirming the presence of a neurogenic bladder. With the availability of sildenafil (see below) to use as a therapeutic trial, such tests are generally reserved for nonresponders who may eventually be considered for surgical placement of a penile prosthesis.

As discussed previously, hormonal abnormalities are frequently detected in chronic kidney disease patients. Useful endocrine tests to evaluate an organic cause of impotence include measurement of plasma LH, FSH, testosterone, and prolactin levels. Only a small percentage of uremic patients will have prolactin levels greater than 100 ng/mL. Imaging studies of the hypothalamic-pituitary region should be performed in patients with levels of greater magnitude in order to exclude the presence of a microadenoma or macroadenoma.

Treatment of Sexual Dysfunction in Uremic Men

The treatment of sexual dysfunction in uremic men is initially of a general nature (Fig. 56.1). One needs to ensure optimal delivery of dialysis and adequate nutritional intake. Administration of recombinant human erythropoietin has been shown to enhance sexual function, likely through the associated improvement in well-being that comes with the correction of anemia, although improvement in the pituitary-gonadal feedback mechanism has also been reported. Controlling the degree of secondary



• **Fig. 56.1** Approach to Sexual Dysfunction in Uremic Men.

hyperparathyroidism with 1,25-dihydroxyvitamin D may be of benefit in lowering prolactin levels and improving sexual function in some patients.

One area that deserves further investigation is the impact of slow nocturnal hemodialysis on sexual function. In a pilot study of patients undergoing dialysis 6 nights per week for 8 hours each night, serum testosterone levels increased in three patients over an 8-week period. Levels of LH and FSH remained unchanged. In a separate study, the percentage of patients who felt that sexual function was a problem declined from 80% to 29% after 3 months of nightly nocturnal hemodialysis.

Patients with normal NPT testing should be evaluated to determine if there is a psychological component to the impotence. If a problem is found, then a trial of psychotherapy is warranted. The effectiveness of antidepressant medications and/or psychiatric counseling in chronic kidney disease patients with sexual dysfunction has not been well studied. Use of antidepressant medications can be problematic because many of these agents can cause sexual dysfunction.

It has become common clinical practice to first administer sildenafil to patients who complain of erectile dysfunction and reserve further workup for only those patients who fail to achieve a therapeutic response. A limited number of studies have been published specifically examining the effectiveness of sildenafil in uremic men with chronic kidney disease. Each of these studies used the International Index of Erectile Function (IIEF) questionnaire as a means to gauge the effectiveness of the therapy. The response rate ranged from 60% to 80%. Sildenafil has similar efficacy in patients treated with either hemodialysis or peritoneal dialysis. It should be emphasized that sildenafil is contraindicated in patients who are currently taking organic nitrates. Caution should also be exercised when prescribing this agent to patients with known coronary artery disease. To limit the possibility of hypotension among dialysis patients, some clinicians recommend the use of sildenafil on nondialysis days.

In patients with low circulating levels of testosterone, correcting the deficit generally results in clinical improvement in other forms of gonadal failure. By contrast, administration of testosterone to uremic men usually fails to restore libido or potency, despite increased testosterone levels and reduced release of LH and FSH. Nevertheless, a trial of testosterone may be warranted in a hypogonadal patient whose primary complaint is decreased libido.

Patients found to have increased circulating levels of prolactin may benefit from a trial of bromocriptine. This dopaminergic agonist has shown some efficacy in improving sexual function, presumably by reducing elevated prolactin levels. However, its usefulness is limited by a relatively high frequency of side effects. Other dopaminergic agonists, such as Parlodel and lisuride, tend to be better tolerated but have only been used in small short-term studies.

Zinc deficiency has been suggested as a cause of gonadal failure. Uremic patients are often deficient in zinc, probably because of reduced dietary intake, zinc malabsorption, and/or possible leaching of zinc by dialysis equipment. In a controlled trial, supplemental zinc resulted in significant increases in plasma testosterone concentration and sperm counts, as well as significant declines in LH and FSH levels as compared to a control group. Potency, libido, and

frequency of intercourse also improved in those given zinc. Normalization of total body zinc may also be effective in correcting uremic hyperprolactinemia. The aggregate data suggest that administration of zinc to zinc-deficient men is a reasonable therapeutic option.

There are additional options for those patients with a neurogenic or vascular cause of impotence who have failed medical therapy to include a trial of sildenafil. One such therapy is a vacuum tumescence device. In one kidney impotence clinic, vacuum tumescence devices were used in 26 impotent patients, all of whom had a normal pituitary-gonadal axis or hypogonadism corrected with testosterone replacement. The device completely corrected penile dysfunction in 19 individuals (73%).

Intraurethral administration of alprostadil (synthetic prostaglandin E_1) provides the delivery of prostaglandin to the corpus cavernosum, resulting in an erection sufficient for intercourse. The drug is supplied in an applicator that is inserted in the urethra. Alprostadil can also be injected into the penis shaft, resulting in vasodilation and inhibition of platelet aggregation. The major side effects of intrapenile alprostadil therapy are penile pain, priapism, and bleeding. Given the presence of platelet dysfunction with uremia, intracavernosal injections should be used with caution in patients with end-stage kidney disease. Surgical placement of a penile prosthesis is typically considered in patients who fail the less invasive first-line treatments.

A well-functioning kidney transplant can restore sexual activity and fertility; however, some features of reproductive function may remain impaired, particularly reduced libido and erectile dysfunction. This improvement occurs in association with normalization of the serum testosterone concentration and, in many patients, an increase in sperm count.

Sexual Dysfunction in Uremic Women

Disturbances in menstruation and fertility are commonly encountered in women with chronic kidney disease, usually leading to amenorrhea by the time the patient reaches end-stage kidney disease. The menstrual cycle typically remains irregular, with scanty flow after the initiation of maintenance dialysis, although normal menses is restored in some women. In others, hypermenorrhagia develops, potentially leading to significant blood loss and increased transfusion requirements. Women on chronic dialysis also tend to complain of decreased libido and reduced ability to reach orgasm.

Indirect determination of ovulation suggests that anovulatory cycles are the rule in uremic women. For example, endometrial biopsies show an absence of progestational effects, and there is a failure to increase basal body temperature at the time when ovulation would be expected. In addition, the preovulatory peak in LH and estradiol concentrations are frequently absent. The failure of LH to rise in part reflects a disturbance in the positive estradiol feedback pathway because the administration of exogenous estrogen to mimic the preovulatory surge in estradiol fails to stimulate LH release. Pregnancy can rarely occur in advanced kidney failure, but some degree of residual kidney function is usually present. As in men with chronic kidney disease, circulating levels of prolactin are increased. The secretion appears autonomous and is resistant to maneuvers designed to stimulate or inhibit its release.

Postmenopausal uremic women have gonadotropin levels as high as those seen in nonuremic women of similar age. The age at which menopause begins in chronic kidney disease patients tends to be decreased when compared to women with normal kidney function.

Treatment of Sexual Dysfunction in Uremic Women

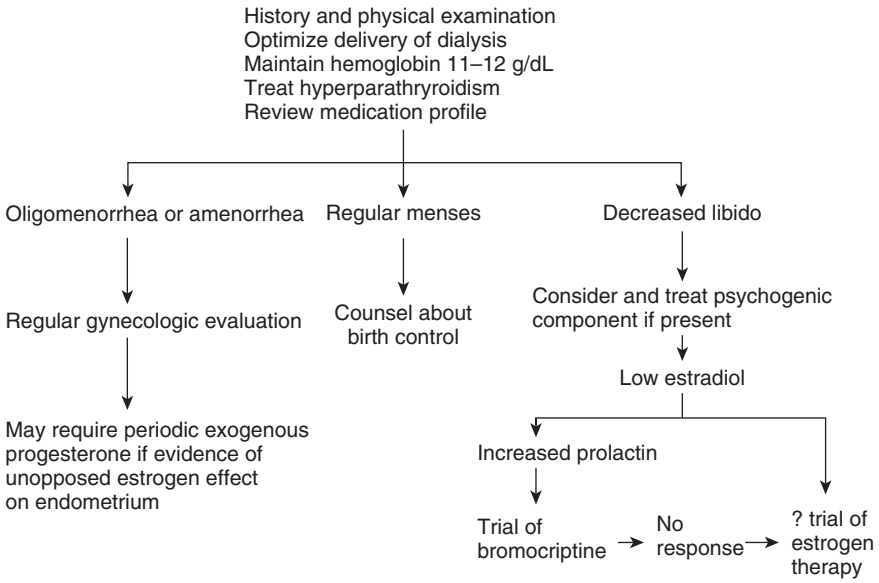
The high frequency of anovulation leads sequentially to a lack of formation of the corpus luteum and failure of progesterone secretion. Because progesterone is responsible for transforming the endometrium into the luteal phase, a lack of progesterone is associated with amenorrhea. For patients who desire to resume menses, administration of a progestational agent during the final days of the monthly cycle is usually successful.

On the other hand, ongoing menses can contribute significantly to the anemia of chronic kidney disease, particularly in those patients with hypermenorrhagia. In this setting, administration of a progestational agent during the entire monthly cycle will terminate menstrual flow. Rarely, a patient may require a hysterectomy for refractory uterine bleeding.

Periodic monitoring by a gynecologist is indicated in women with chronic kidney disease. It is unknown whether the usual absence of menses in these women predisposes to the development of endometrial hyperplasia and possible carcinoma. Because these patients are often anovulatory, there is no disruption of the proliferative effect of estrogen by the release of progesterone. Some women may require administration of a progestational agent several times per year to interrupt the proliferation induced by unopposed estrogen release (Fig. 56.2).

While pregnancy can rarely occur in women on thrice-weekly chronic dialysis, restoration of fertility as a therapeutic goal should be discouraged. More intensive dialysis as achieved by daily nocturnal hemodialysis may allow for improved fertility. In comparison, the abnormalities in ovulation can usually be reversed and successful pregnancy achieved in women with a well-functioning kidney transplant. Uremic women who are menstruating normally should be encouraged to use birth control.

Studies addressing treatment of decreased libido and sexual function in uremic women are lacking. Amenorrheic hemodialysis patients may have low estradiol levels that can secondarily lead to vaginal atrophy and dryness and result in discomfort during intercourse. Such patients may benefit



• **Fig. 56.2** Approach to Sexual Dysfunction in Uremic Women.

from local estrogen therapy or vaginal lubricants. Low-dose testosterone may be effective in increasing sexual desire but is rarely used secondary to potential toxicity. Use of a transdermal testosterone patch has been shown effective in improving libido in nonuremic surgically menopausal women; however, this therapy is not yet approved. Bromocriptine therapy in hyperprolactinemic patients may help in restoring sexual function but has not been well studied. Estrogen supplementation may improve sexual function in patients with low circulating estradiol levels. Successful transplantation is clearly the most effective means to restore normal sexual desire in women with chronic kidney disease.

Recommended Reading

Barua M, Hladunewich M, Keunen J, et al. Successful pregnancies on nocturnal home hemodialysis. *Clin J Am Soc Nephrol.* 2008;3:392–396.

The paper describes a small number of women who had successful pregnancies while receiving long dialysis times associated with nocturnal hemodialysis. There were seven pregnancies in five women who were being treated with nocturnal hemodialysis, with dialysis times averaging 36 hours/week. The paper suggests that nocturnal hemodialysis may allow for improved fertility and that delivering a live infant at a mature gestational age is feasible for patients on such therapy.

Collaborative Depression and Sexual Dysfunction in Hemodialysis Working Group. Prevalence and correlates of erectile dysfunction in men on chronic haemodialysis: a multinational cross-sectional study. *Nephrol Dial Transplant.* 2012;27:2479–2488.

The authors conducted a multinational cross-sectional study in 946 men on hemodialysis within a collaborative network examining erectile dysfunction and depressive symptoms. Eighty-three percent reported erectile dysfunction and 47% reported severe erectile dysfunction. Only 4% of those with erectile dysfunction were receiving pharmacologic treatment, suggesting that most men on hemodialysis experience erectile dysfunction and are untreated.

Holley J, Schmidt R. Changes in fertility and hormone replacement therapy in kidney disease. *Adv Chronic Kidney Dis.* 2013;20:240–245.

An excellent article describing what is known regarding changes in fertility and hormone replacement therapy in patients with chronic kidney disease. The authors emphasize that although infertility is common in these patients, it is poorly studied, as is the issue of hormone replacement therapy.

Mor M, Sevick M, Shields A, et al. Sexual function, activity, and satisfaction among women receiving maintenance hemodialysis. *Clin J Am Soc Nephrol.* 2014;9:128–134.

An analysis of 125 women on hemodialysis in which 81% reported that they were not sexually active, consistent with a low level of sexual activity noted in other studies. Importantly, these investigators looked at the reasons for sexual inactivity and patient satisfaction with their current level of sexual functioning. The main reasons cited by patients for lack of sexual activity in this study were lack of a partner (39%) and lack of interest (43%). Actual sexual difficulties were cited by only 2% of women, suggesting that true sexual dysfunction is uncommon in this patient population.

Navaneethan S, Vecchio M, Johnson D, et al. Prevalence and correlates of self-reported sexual dysfunction in CKD: a meta-analysis of observational studies. *Am J Kidney Dis.* 2010;56:670–685.

The authors conducted a systematic review and meta-analysis of the literature (50 studies and 8343 patients) examining sexual dysfunction in men and women with CKD using validated tools. The summary estimate of erectile dysfunction in men with CKD was 70%. In women, the reported prevalence of sexual dysfunction was assessed in only 306 patients from two studies and ranged from 30% to 80%. The authors conclude that sexual dysfunction is highly prevalent in both men and women with CKD, especially among those on dialysis.

Pertuz W, Castaneda D, Rincon O, Lozano E. Sexual dysfunction in patients with chronic kidney disease: does it improve with kidney transplantation? *Transplant Proc.* 2014;46:3021–3026.

The authors conducted a MEDLINE search examining the impact of kidney transplantation on sexual function before and after the procedure. In the analysis, 40%–78% of male patients with a kidney

transplant report a sense of improvement on global sexual function, whereas 25%–30% of female patients of reproductive age report improvement in sexual performance and decrease of menstrual cycle alterations. Fewer than 10% of patients reported a decrease of sexual satisfaction. The authors conclude that kidney transplantation improves sexual functioning by improving sexual desire and overall sexual satisfaction.

Pizzol D, Xiao T, Yang L, et al. Prevalence of erectile dysfunction in patients with chronic kidney disease: a systematic review and meta-analysis. *Int J Impot Res.* 2021;33(5):508–515.

The authors performed a meta-analysis including 34 studies and almost 6000 participants and found erectile dysfunction affected approximately three-fourths of the chronic kidney disease population.

Solak Y, Atalay H, Kan S, et al. Effects of sildenafil and vardenafil treatments on sleep quality and depression in hemodialysis patients with erectile dysfunction. *Int J Impot Res.* 2011;23:27–31.

This is a study examining the effects of sildenafil and vardenafil on sleep quality and depression in 32 men on hemodialysis with erectile dysfunction. The phosphodiesterase-5 inhibitors caused a significant improvement in sleep quality and depression in this cohort of hemodialysis patients.

Strippoli G, for the Collaborative Depression and Sexual Dysfunction (CDS) in Hemodialysis Working Group. Sexual dysfunction in women with ESRD requiring hemodialysis. *Clin J Am Soc Nephrol.* 2012;7:974–981.

A large, cross-sectional study of 1472 women with ESRD undergoing hemodialysis evaluating the prevalence and correlates of sexual dysfunction in advanced kidney disease. Of the respondents, 84% reported sexual dysfunction. Women with a partner were less likely to report sexual dysfunction than those without a partner. Sexual dysfunction was independently associated with age, depressive symptoms, less education, menopause, diabetes, and diuretic therapy. Nearly all women who were not wait-listed for a kidney transplant and were living without a partner reported sexual dysfunction.

Turk S, Solak Y, Kan S, et al. Effects of sildenafil and vardenafil on erectile dysfunction and health-related quality of life in haemodialysis patients: a prospective randomized crossover study. *Nephrol Dial Transplant.* 2010;25:3729–3733.

The authors studied 32 men on maintenance hemodialysis and found that use of either sildenafil or vardenafil was effective in improving health-related quality of life and erectile dysfunction in this patient population.

Vecchio M, Navaneethan S, Johnson D, et al. Treatment options for sexual dysfunction in patients with chronic kidney disease: a systematic review of randomized controlled trials.*Clin J Am Soc Nephrol.* 2010;5:985–995.

The authors conducted a MEDLINE and Cochrane Trial Registry search to examine the benefits and harms of existing interventions for treatment of sexual dysfunction in CKD patients. Phosphodiesterase-5 inhibitors (PDE5i) compared with placebo significantly improved measures of erectile function. End-of-treatment testosterone levels were not significantly increased by addition of zinc to dialysate, but oral zinc improved end-of-treatment testosterone levels. There was no difference in plasma LH and FSH level at the end of the study period with zinc therapy. The authors conclude that PDE5i and zinc are promising interventions for treating sexual dysfunction in CKD.

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Pregnancy in Dialysis Patients

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Introduction: A Historic Perspective

When the first successful pregnancy in a woman on hemodialysis was reported in 1971 by Confortini and coworkers, the report elicited more skepticism than enthusiasm, and some nephrologists felt that emphasizing this exceptional occurrence could lead to the wrong expectations and might even be detrimental. In 1975, an editorial in *The Lancet* stated, "Children of women with renal disease used to be born dangerously or not at all—not at all if their doctors had their way."

Having a child while on dialysis is still a very rare event, albeit no longer such an exceptional one, and the interest in this particular niche of dialysis management has implications that go far beyond the technical aspects. These implications involve the concept of dialysis efficacy, as well as social aspects, including the different attitudes towards pregnancy in diverse cultural settings and the limits of dialysis availability in highly as well as poorly resourced countries.

In this chapter, we will summarize what we know and agree on, and what we do not know, or is a matter of controversy, on the main aspects of dialysis in pregnancy: epidemiology and main maternal-fetal results, indications for dialysis start in pregnancy, dialysis schedules, nutritional approaches, psychological aspects, and data on children of on-dialysis mothers.

Evidence-Based Medicine and Pregnancy on Dialysis: Methodological Insights

Evidence regarding pregnancy on dialysis is limited and mainly derived from observational studies. Obviously, pregnancy itself cannot be randomized; for evident ethical reasons, randomization of any kind of treatment in pregnancy is complex, and ethical barriers are more often present in this context than in other areas of nephrology and dialysis. As a consequence, we do not have, nor do we expect to have in the future, randomized controlled trials on dialysis duration, frequency, schedule, or on obstetric monitoring policies.

Rare events are, by nature, either reported by large multicenter sources, registries or cross-linked databases or in small series or case reports. Large series frequently lack clinical details and are often highly heterogeneous. Case reports and small series are more likely to be affected by reporting and publication biases: the happy ending of a rare event prompts communication, but the opposite is true in the case of catastrophic events, such as the loss of mother and/or child. As such, case reports and small series should be taken as a marker of what is possible but can be hard to translate into the true probability of success.

The "physiological" lack of randomized controlled trials, the rarity of the event, and the heterogeneity of the sociocultural background and clinical approaches are also reflected by the limited number of available guidelines or best practices. To the best of our knowledge, only the Italian Society of Nephrology dedicated one of its five best practices on pregnancy and the kidney to pregnancy on dialysis, while one guideline from the U.K. is dedicated to the entire topic of chronic kidney disease (CKD) in pregnancy and includes the dialysis issue. Conversely, the National Institute for Health and Care Excellence (NICE) Guidelines on intrapartum care for women with existing medical conditions or obstetric complications and their babies dedicate a short paragraph to acute kidney injury and CKD.

Epidemiologic Aspects of Pregnancy on Dialysis

Frequency of Pregnancy in Dialysis Patients

Since pregnancy is considered a rare, if not exceptional, occurrence on dialysis, many dialysis registries do not record this event, the exception being the Australian and New Zealand Registry, which is now one of the most important sources of epidemiological information in this regard. However, early pregnancy abortions or miscarriages may escape being recorded, large-scale and systematic information on conception is not available, and epidemiological data mainly regard pregnancies that go beyond the second trimester.

Within these limits, two concordant studies, one from Italy and one from Australia, albeit with a different study design (nationwide survey in Italy and registry data in Australia), suggest that there is a 1:10:100 gradient in birth rates between dialysis, kidney transplantation, and the general population. In other words, the probability that a woman of childbearing age on dialysis will deliver is about 1:100 compared to the overall population of the same geographic area. While the two studies come from culturally and geographically different settings, they were both performed in countries in which dialysis, and related care, is available without restriction for all patients. Less is known about those countries in which dialysis access is nonuniversal.

Recent data from the United States report an increase of pregnancies in women on renal replacement therapy, both on dialysis and after kidney transplantation, in the period 2002–15. The reasons for this phenomenon are not clear, and the fact that it involves both dialysis and kidney transplantation suggests that the increase is not merely driven by the better results obtained in dialysis and that different sociocultural issues are involved.

The importance of cultural and social aspects has been highlighted by several sources. Indirect clues come from the increasing number of pregnancies reported in patients on dialysis in Latin America or the Arab world, where yearly pregnancy rates on dialysis may be higher. Indeed, in both settings, the attitude towards pregnancy is characterized by a cultural drive towards large families and a lower influence on social life by "invisible diseases," such as end-stage kidney disease (ESKD).

Recent data from a study performed in a large U.S. cohort between 2005 and 2013 with an unexpectedly high pregnancy rate (17.8 per 1000 patient years) showed pregnancy was associated with belonging to an ethnic minority or living in a low-income area. In keeping with a higher probability of becoming pregnant for a woman from a disfavored milieu, one-third of these pregnancies were "lost to follow-up." The intriguing association between pregnancy and belonging to a low-income, minority strata of the population, which is in turn associated with lower adherence to the medical prescription and counseling, raises the question of whether this reflects a difference in reference values, such as the importance of large families or a lower probability of being influenced by the health care team, whose opinions on pregnancy in dialysis are frequently reductive.

Notwithstanding the sociocultural aspects, according to the few large-scale reports, pregnancy is more frequent, and its outcomes are more often favorable when conception occurs before the start of dialysis or in the first months/years after dialysis initiation. The presence of some residual kidney function or, at least, residual diuresis is associated with better outcomes. However, successful pregnancies have also been reported in women with a long dialysis vintage on peritoneal, as well as on hemodialysis (as will be further discussed regarding dialysis schedules) and in the context of all types of kidney diseases, including those, like lupus nephropathy, which are often associated with poorer outcomes.

This complex network of sociocultural and medical issues may be summarized as follows.

What we know:

Pregnancy on dialysis is a rare event.
The frequency of delivery may be estimated at about 1:100 with respect to the overall population of the same geographic area, at least in highly-resourced countries.
While pregnancies are more frequently reported and more frequently successful in women who have recently started dialysis and who have some residual kidney function, successful pregnancies have been reported in women affected by all kidney diseases, at different ages and dialysis vintages.

What we do not know:

What the incidence of early fetal loss and elective pregnancy termination is.
What the differences in fertility and delivery rates around the world are.
What the influence of the social and cultural background is.
What the role of medical counseling in favor or against pregnancy is.

Maternal and Fetal Outcomes

The likelihood that a pregnancy in a dialysis patient ends with the "baby in mother's arms" is increasing and strongly depends upon the dialysis schedule, as will be shown in the following paragraphs.

Until the new millennium, the reported chances that pregnancy in a dialysis patient would end successfully progressively increased from 23% in a report by the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA) in 1980, comprising 115 pregnancies in dialysis, to approximately half of the pregnancies in a nationwide series published in 1998. In 2008, a systematic review focusing on the outcomes in the new millennium retrieved only 90 cases, with an overall probability of a healthy offspring ranging from 50% to 100% (overall 76.3%). After that, reports sharply increased, and about 1000 pregnancies in dialysis patients were reported between 2000 and 2020. The most recent systematic review available in this issue, published in 2016, gathered almost 700 pregnancies in the new millennium and confirmed a success rate of about 80%.

However, the reporting bias might be critical, and the available literature can be considered informative mainly on cases that go beyond the first trimester, since it is likely that information on early miscarriages is missing.

In keeping with what is observed in non–dialysis-dependent CKD, preterm delivery is almost the rule (83% in the meta-analysis), and the birth of a small for gestational age baby is likewise frequent (over 30% of cases on hemodialysis in the same review; the incidence is higher on peritoneal dialysis [PD] and was rated at about 60%).

There seems to be no excess mortality in mothers who had a baby while on dialysis versus other women on dialysis;

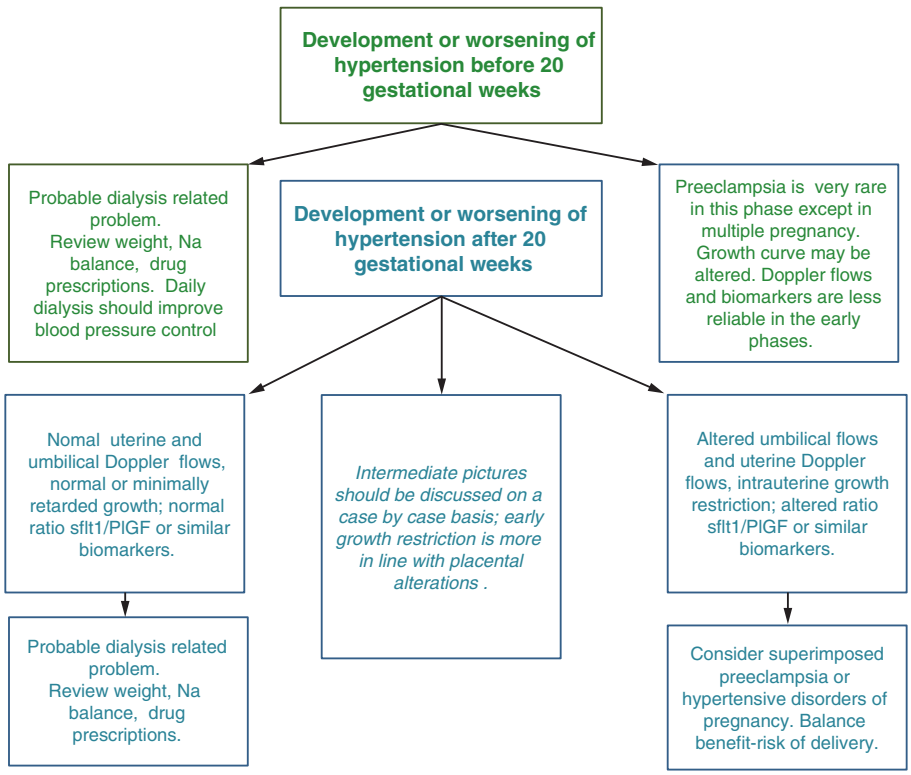
however, the long-term impact of having had a pregnancy, against the background of increased mortality in dialysis patients, is not known.

The risk of developing or worsening hypertension during pregnancy is high. Defining preeclampsia in dialysis patients is, however, difficult, if not impossible. In any case, against the background of kidney disease, we are dealing with "superimposed preeclampsia," and furthermore, proteinuria is not a reliable marker in this context, even in patients with residual kidney function. Moreover, attributing new development or worsening of hypertension to pregnancy is difficult due to the interference between blood pressure and water and sodium homeostasis. Moreover, the biomarkers that are increasingly being employed in assessing the risk of preeclampsia should be considered with skepticism in dialysis patients since their behavior is not fully known, and relying on laboratory data alone may be misleading. Taking into account these caveats, we suggest monitoring s-flt1 and placental growth factor (PlGF) starting in the 20th pregnancy week (in many countries there is a ban on earlier testing), as these biomarkers may indeed reflect placental health, and their normality may point clinical management toward pharmacological intervention and modulation of the dialysis prescriptions. A putative algorithm, merging utero-placental flows, fetal growth, and biomarkers, is reported in Fig. 57.1.

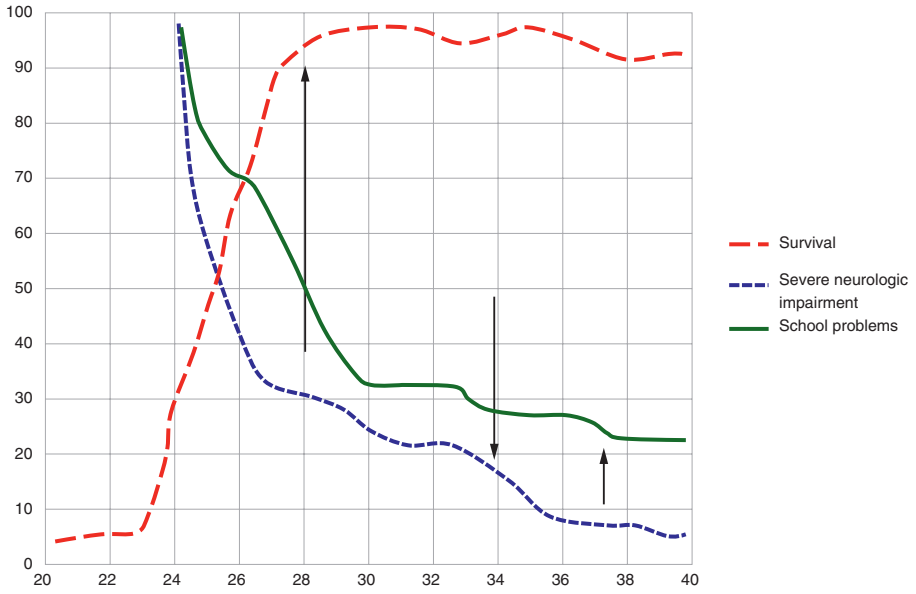
Once more, in keeping with the data reported in the population with CKD not on dialysis, there is no evidence of an increased risk of congenital abnormalities other than those expected in cases of genetic kidney diseases (including, among others, polycystic kidney diseases and congenital anomalies of the kidney and urinary tract).

Current evidence suggests that the prognosis of children born to on-dialysis mothers is mainly linked to prematurity and intrauterine growth restriction: Fig. 57.2 is a remake of a classic illustration of the association between prematurity and neurological deficits, which can be of use in counseling. Besides some neurological disorders associated with prematurity (in the most severe cases presenting with cerebral hemorrhage), being born very preterm or small for gestational age, especially if linked to intrauterine growth retardation (Fig. 57.3), is associated with an increased risk of developing hypertension, obesity, metabolic syndrome, or CKD in adulthood. This observation may be of particular concern for families already faced with the challenges of CKD. The reasons behind this association are not fully understood; however, not attaining an adequate number of nephrons provides the main physiopathological background for the future development of hypertension and kidney disease, while late maturation of fat tissue may be at the basis of the increased risk of obesity and metabolic syndrome. The risks do not seem to be different in on-dialysis mothers with respect to other situations with similar degrees of prematurity or growth restriction; however, the evidence is only indirect and fragmentary.

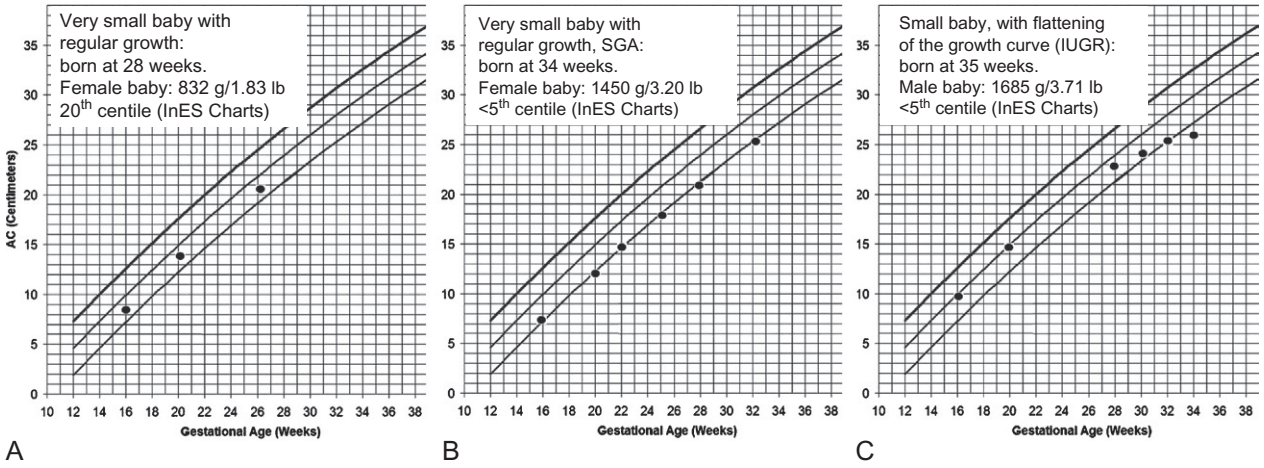
We have only very limited information on the health of children born to on-dialysis mothers. Psychosocial health was analyzed in only one study and seemed comparable with the general population. Another study analyzed kidney health, leading to the identification of an increased risk of albuminuria, whose long-term effect on kidney health remains to be assessed.



• **Fig. 57.1** A proposed diagnostic algorithm in the case of development or worsening of hypertension in pregnancy in a dialysis woman.



• **Fig. 57.2** Patterns of probability of survival and of risk of major and minor neurologic deficits in premature babies.



• **Fig. 57.3** Patterns of Small Babies. (A) Preterm baby regularly grown, normal for gestational age. (B) Preterm baby, regularly grown, small for gestational age. (C) Preterm baby with progressive intrauterine growth restriction and flattening of the growth curve.

Table 57.1 reports the main elements associated with a favorable prognosis in pregnancies in on-dialysis mothers; however, it has to be underlined that successful pregnancies have been reported in all types of kidney disease, with and without residual kidney function and on all dialysis modalities. The success rate is indeed more closely linked to the intensity of dialysis than to the baseline clinical characteristics of the mother; thus, attention has shifted to dialysis management, as will be further discussed.

What we know:

A successful pregnancy in a dialysis patient, defined as "baby in mother's arms," meaning that mother and child are both well and returning home, is possible and is increasingly frequent (over 75% of cases).

There is no excess mortality after delivery for an on-dialysis mother.

There is no excess of malformations in children of on-dialysis mothers (besides the presence of genetic diseases leading to kidney failure in the mother).

Preterm delivery is almost the rule (over 80%), and intrauterine growth restriction is present in about half of the cases;

A successful pregnancy is possible in all kidney diseases, both on PD or hemodialysis and also with a long dialysis vintage; however, younger age, short dialysis vintage, residual kidney function, and normal blood pressure are probably associated with better outcomes.

The short-term risks for children are linked to prematurity and intrauterine growth restriction; the neurological risks are mainly associated with the degree of prematurity.

Prematurity and intrauterine growth restriction are associated with metabolic syndrome, hypertension, and CKD

TABLE 57.1 Prognostic Elements of Pregnancy on Dialysis

	What We Know	What We Do Not Know—Comments
Residual kidney function	Scattered data suggest that the presence of good residual kidney function is associated with better pregnancy outcomes.	The differences in residual function may be offset by intensive dialysis. If this is not the case, the differences may be due to lower accumulation of larger molecules (the "middle molecules," only partially cleared by dialysis) or to lesser volume changes during hemodialysis.
Short dialysis vintage	Lower uremia-related comorbidity and higher residual kidney function are expected in these patients.	The role of each element is difficult to disentangle.
Non-immunologic disease	Prognosis of pregnancy in CKD is overall better in nonimmunologic diseases; hence, the same may be the case in on-dialysis patients.	Dialysis is often considered as offsetting the effect of immunologic diseases. We do not know if this is true in pregnancy.
Younger age	Pregnancy-related risks increase with age. It is reasonable to infer that younger dialysis patients, who usually also have a shorter exposure to uremia, may have a better prognosis.	There are no specific data on the age effect in on-dialysis patients. Indeed, age is an important issue in pregnancy on renal replacement therapy (see text—ethical issues)
Normotension	Baseline blood pressure levels are important determinants of the prognosis of CKD pregnancies.	Hypertension in dialysis patients is usually volume dependent, and its control is easier on daily dialysis. The role of the different pathogenesis of hypertension (volume dependent versus pregnancy induced) is not clear.
Good compliance	Adhering to and understanding prescriptions are fundamental for managing the demanding dialysis schedule.	The different outcomes reported in settings where patients are referred when they specifically want to have a child, and unwanted pregnancies may underline the importance of the compliance issue.

CKD, Chronic kidney disease.

in adulthood; these risks do not seem to be different in on-dialysis mothers with respect to other situations with similar degrees of prematurity or growth restriction.

What we do not know:

We have only partial data on early pregnancy loss, so our knowledge of the first phases of pregnancy is limited.

We have no evidence allowing quantification of the importance of factors that are known to affect pregnancies in CKD patients not on dialysis (age, kidney disease, etc.).

We have very limited information on the long-term health of children of on-dialysis mothers.

Diagnosis of Pregnancy, Prenatal Screening, and Assisted Fertilization in Dialysis Patients

The term "diagnosis of pregnancy" may sound funny at first since pregnancy is not a disease, and its signs are usually rapidly evident. The latter may, however, not be true in young women on dialysis and for several reasons: the hormonal derangements commonly observed in ESKD are usually associated with irregular menses, and a missed menstrual cycle does not immediately evoke pregnancy; intermenstrual bleeding is frequent and may mimic menses; the idea that dialysis is associated with infertility may reduce awareness of the possibility of getting pregnant. Indeed, in the Italian series, more than half of recorded pregnancies were unplanned, and similar results were reported in the United States. On the other hand, in the Canadian experience, some women are "prepared" for pregnancy by increasing dialysis frequency. While there is little published evidence to support this approach, the rationale is sound since intensive hemodialysis is able to restore the hormonal milieu, presumably facilitating pregnancy.

The background levels of beta-human chorionic gonadotropin (beta-hCG), which is usually employed in the confirmation of pregnancy, are increased in dialysis patients, even in nonpregnant ones. Beta-hCG is produced in small amounts in men and nonpregnant women, primarily by the anterior pituitary gland; beta-hCG is a "middle molecule," a term that indicates a molecule of molecular weight between 500 and 60,000 Daltons, which accumulates in severe CKD.

In this context, pregnancy dating mainly relies on echography signs. Being on dialysis does not affect the initial phases of embryonic development; therefore, early ultrasound assessment is as reliable as in other pregnancies. Conversely, in

later pregnancy phases, in which pregnancy is often not discovered in dialysis patients, the onset of intrauterine growth restriction may interfere with pregnancy dating, which can, in turn, complicate pregnancy management.

Experience in prenatal screening is limited in these pregnancies.

Amniocentesis and chorionic villus sampling remain the gold standard.

Since amniocentesis and chorionic villus sampling are considered as bearing a 1% risk of miscarriage, other options are increasingly being explored, in particular, planned and often long-awaited pregnancies. Noninvasive prenatal screening for Down syndrome has a high rate of false positives due to the increase in the background levels of both beta-hCG and pregnancy-associated plasma protein A (PAPP-A). PAPP-A is a biomarker of inflammation and is associated with cardiovascular and all-cause mortality in dialysis patients.

Screening for fetal chromosomal derangements through cell-free circulating DNA (cfDNA) in the maternal plasma represents an appealing potential alternative for patients on dialysis, but there is only very little experience in this regard. Indeed, on account of its molecular weight, cfDNA could be at least partially cleared by hemodiafiltration or by hemodialysis with highly permeable membranes. In addition, little is known about maternal cfDNA release during dialysis (i.e., acute and chronic inflammation as in peritonitis, immune and autoimmune diseases, vascular diseases, etc.), which could affect the maternal to placental cfDNA ratio (the so-called fetal fraction [FF]) and cfDNA test sensitivity. While waiting for further data, if this approach is chosen, its limits should be highlighted, and collaboration with an experienced obstetrical team is mandatory.

While a discussion on contraceptive use in dialysis is beyond the scope of this chapter (we may suggest referring to the recent Italian best practice for contraception in kidney diseases for details), it is important to remember that this issue should be systematically touched upon in dialysis patients in order to identify the most suitable birth control strategy.

In women who wish to get pregnant, besides providing intensive dialysis and monitoring hyperprolactinemia, baseline assessment of beta-hCG may be of interest to allow for reliable monitoring of the first phases of pregnancy; we suggest gathering at least two to three measurements since the behavior of this middle molecule in dialysis patients is only partially known. Furthermore, women should be warned that they need to report not only the classic symptoms of nausea and breast tenderness but also any reduction in blood pressure, fatigue, and/or increased need for erythropoiesis-stimulating agents.

Assisted fertilization is increasingly being employed in situations in which fertility is reduced, in particular when the mother's age is high, and the ovarian reserve is low. Reports on dialysis patients are very limited and, as occurs with rare events, reporting and publication biases are once again substantial, limiting the information to favorable cases; conversely, women may not wish to openly discuss these issues, and underreporting may also be an issue. Despite these caveats, happy endings have been reported, at least confirming feasibility, but without allowing for any conclusions to be made regarding risks and success rates.

The potential contraindications in women on dialysis are mainly linked to the hormonal conditioning that is usually part of the assisted fertilization techniques. Indeed, the features of ovarian hyperstimulation syndrome (hyperhydration, edema, ascites, and hypercoagulability) may be particularly challenging in dialysis patients. Attention to fluid management, avoiding overzealous dehydration since the main weight gain is due to interstitial edema, and care in normalizing blood pressure is particularly relevant in these phases. In vitro fertilization may be proposed on spontaneous cycles with lower risks but also with lower chances of success. Once more, there is a strong need for a coordinated nephrology and obstetrical work-up.

What we know:

Detecting (or "diagnosing") pregnancy in dialysis patients may be difficult by the standard tests.

Ultrasound pregnancy dating is reliable in the first weeks but may later be affected by intrauterine growth restriction.

The gold standard for detection of chromosomal abnormalities remains amniocentesis or chorionic villus sampling, bearing, however, a risk of miscarriage.

Assisted fertilization may result in successful pregnancies, even if only scarce experience is available on this issue.

What we do not know:

Noninvasive prenatal screening for Down syndrome, an alternative to amniocentesis or chorionic villus sampling in the overall population, has not been sufficiently explored in dialysis patients.

The risk of ovarian hyperstimulation in assisted fertilization may be higher in dialysis patients, but its incidence and severity are not known.

If and how intensive dialysis may be used to improve fertility are not known, even if this is a logical clinical approach.

When to Start Dialysis in Pregnancy

Very few issues are more controversial in the field of obstetric nephrology than the indications to start dialysis in pregnancy.

These indications need to balance and combine several different issues.

The first one regards the superior results obtained in women on chronic dialysis who underwent an intensive hemodialysis strategy. For this reason, we will only refer to hemodialysis starts in pregnancy, discussing the option of continuing PD in pregnancy in the next paragraph.

The second point is the caution toward the early start of dialysis that changed the approach to dialysis initiation in the nonpregnant dialysis population.

The third issue is the possibility of using nutritional management to delay the need for dialysis start, both in the overall population and in pregnant women.

Of interest, the team with the most experience in intensive dialysis in pregnancy (the Toronto group in Canada) and the team with the most experience in nutritional management to delay dialysis starts (the Torino group in Italy) are presently collaborating in a multicenter study to compare the results of these two nonmutually exclusive approaches. While waiting for the results of such a study, this chapter critically summarizes the main experiences and matters of discussion.

An important point concerning dialysis starts regards the way kidney function is analyzed in CKD pregnancy. In fact, in pregnancy, there is no agreed-upon formula for assessing the estimated glomerular filtration rate (eGFR) from serum creatinine, and even the use of creatinine clearance, based upon 24-hour urine collection, is not devoid of problems, in particular when it comes to a clearance of less than 15 mL/min. In this context, some authors suggest that the estimate of kidney function is more reliable if the mathematic mean between urea and creatinine clearance is employed. However, urea clearance is affected by diet, with a risk of underestimation, in particular in patients with lower protein intake.

Urea levels are currently employed as markers of adequacy in the intensive dialysis schedules of pregnancy; as a consequence, the definition of the need for dialysis starts as determined by urea levels is increasingly frequent. This pragmatic choice is not supported by sound evidence, and also, on account of the different normal values employed, the data in the literature are somehow heterogeneous. A reasonable approach is to combine more than one measurement, including urea (or blood urea nitrogen [BUN]) levels, urea and creatinine clearances based on 24-hour urine collection, and the analysis of other elements (such as blood pressure and hydration status, nutritional status, acidosis, calcium–phosphate and parathyroid hormone [PTH] balance, anemia monitoring, etc.) that are usually employed to establish the indications to start dialysis in the nonpregnant CKD population.

There is no doubt that once dialysis is started, intensive hemodialysis is associated with the best results. The shift from "as much dialysis as possible" to "dialysis as early as possible" may be logical, and it is on these bases that some authors suggest starting dialysis in pregnancy at the urea level that corresponds to the predialysis target indicated in the Toronto studies. While urea levels are highly dependent upon diet and on the metabolic pattern of each individual, a urea level of about 100 mg/dL or a BUN of about 50 may correspond to an eGFR between 20 and 30 mL/min, much higher than the eGFR considered for early (about 15 mL/min) or late (less than 6–8 mL/min) dialysis start.

Indeed, the indications for dialysis start are presently shifting toward a policy of "intent to defer" dialysis initiation, considering that the early start of dialysis seems to be associated with more harm than good, at least in the usual population of elderly and high-comorbidity patients. The growing evidence on incremental dialysis start suggests that a stepwise approach may limit morbidity and reduce the loss of residual kidney function, one of the elements more closely associated not only with survival on dialysis but also with successful pregnancies in dialysis patients.

We strongly believe that, outside of the context in which dialysis is needed to allow better volume and blood pressure management, the benefits of renal replacement therapy on pregnancy outcomes should be weighed on an individual basis versus the potential threats of catheter-related complications if dialysis is started with a central venous access of the surgical intervention for fistula placement and the overall dialysis-related morbidity. The risk-benefit balance may also be modulated by the phases of pregnancy and in settings with or without easy access to dialysis treatment (Fig. 57.4).

The third element that could be integrated into this discussion is diet.

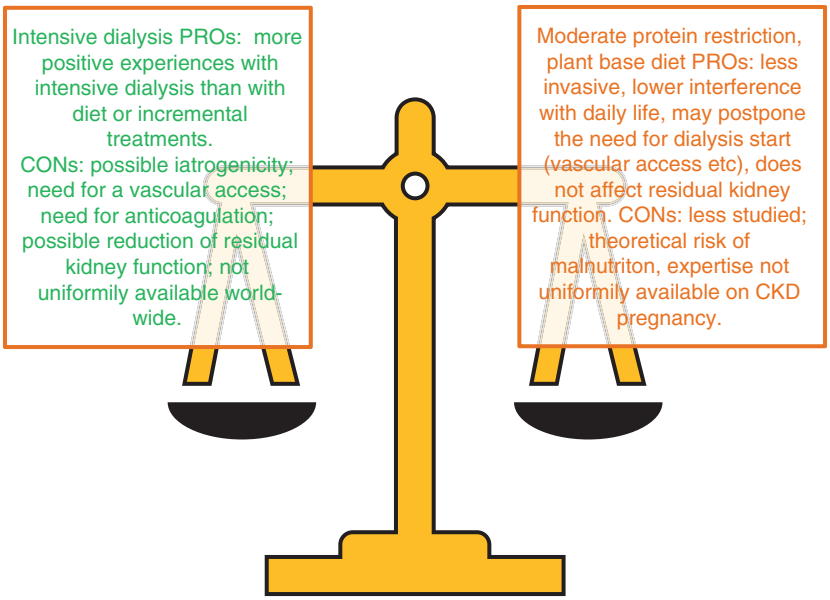
The rationale for integrating the nutritional management of advanced CKD in pregnancy with the choice to start dialysis in pregnancy derives from acknowledging the strict relationship between urea levels and pregnancy outcomes on intensive hemodialysis.

Since dietary protein intake is the main determinant of urea levels, a diet that merges moderate protein restriction with the attainment of the caloric goals and that shifts from animal to mainly plant-based food, with attention to the food quality (including avoiding prepared, canned, or preserved food), may help postpone the need to start dialysis in pregnancy. This experience, mainly carried out by the Torino and the Mexico City teams, may be of particular interest in cases in which the evolution of kidney disease is slow, and the patient shows good compliance. The lack of vascular access or the limited access to chronic renal replacement therapy may also weigh in the choice to attempt nutritional management before elective dialysis starts. Of note, in carefully monitored cases with advanced CKD, the use of such a plant-based, moderately protein-restricted diet has been associated with better preserved fetal growth as compared with unrestricted diets. However, to overcome the risk of malnutrition, dietary management needs to be integrated with strict clinical and laboratory follow-up, including check-ups at least as frequent as those prescribed in patients managed with an early dialysis approach. These options may be further combined in an incremental dialysis start (Fig. 57.4).

On account of the clinical and psychological complexity and of the relevance for the quality of life of the patients, our current recommendations favor a personalized approach to dialysis starts, in the absence of clear signs of uremia, electrolyte derangements, or hydro-electrolyte load, considering the availability of dialysis, the availability of nutritional management, the experience of the team, and, of course, the patient's choices.

While, for the reasons mentioned earlier, we cannot set specific cut-offs for the discussion on dialysis start, we suggest that the alternative options be discussed at least in the eGFR window of 10–30 mL/min.

Conversely, the grim experiences where a clearly needed dialysis start is postponed only for logistic reasons or for the lack of the patient's adherence, as reported from Mexico,



• **Fig. 57.4** Start of Dialysis in Pregnancy: Pros and Cons. *CKD*, Chronic kidney disease.

demonstrate that once dialysis is needed, it should be started promptly to try to improve maternal and fetal outcomes.

What we know:

Evaluation of kidney function in pregnancy is challenging, and different tests should be employed to define it.

Dialysis may be needed in pregnancy, and its start is not associated with side effects other than those observed even out of pregnancy.

A carefully monitored, plant-based, moderately protein-restricted diet may allow postponing dialysis start in pregnancy without detrimental effects on fetal growth.

What we do not know:

Whether there is a single cut-point for dialysis starts in pregnancy and what it is.

Whether dialysis in pregnancy, in the presence of relevant residual kidney function, has to be started at full doses or in an incremental way.

Whether there are differences in the results of the short-term (pregnancy duration, fetal growth) and long-term outcome of the offspring according to the chosen earlier or later dialysis start.

Whether there are differences, especially in the range of the 10–30 mL/min of eGFR, between pregnancy outcomes employing a well-conducted nutritional assessment and an intensive dialysis schedule.

Dialysis Management in Pregnancy

Hemodialysis or Peritoneal Dialysis in Pregnancy?

No prospective or randomized studies have compared PD and hemodialysis in pregnancy; feasibility and ethical issues make it unlikely that one will ever be carried out.

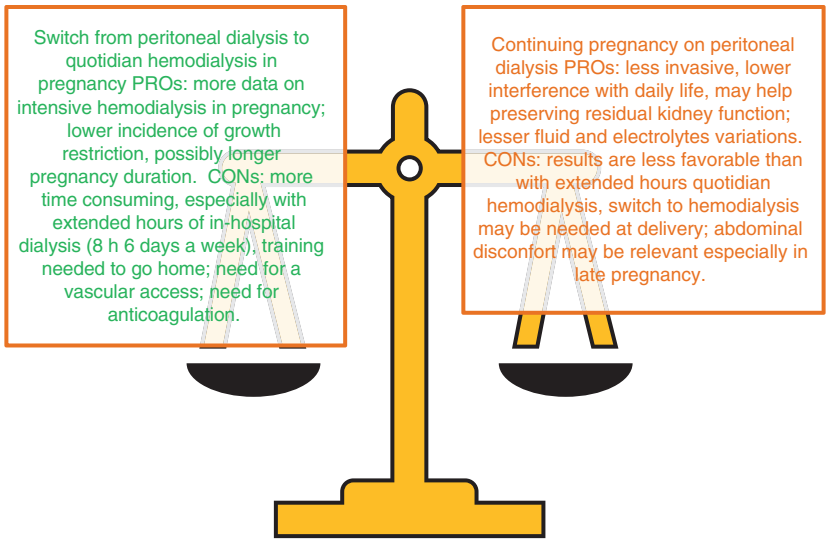
A lower number of pregnancies is reported on PD; this is at least, in part, a reflection of the lower prevalence of this technique. However, the possibility of a negative effect of the lower dialysis efficiency or mechanical elements should be taken into account.

The approach to PD may be different if pregnancy occurs in a woman who is already on PD or if PD is chosen as the option for starting dialysis in pregnancy.

As for dialysis starts, as previously discussed, considering that the best results have so far been obtained with intensive, extended-hours hemodialysis, the current evidence, albeit incomplete, favors starting hemodialysis and considering a switch to PD only after delivery. Such a policy is also indirectly supported by the dismal prognosis of women with acute kidney injury, treated by PD during pregnancy, mainly in under-resourced settings.

Conversely, there is no sound evidence to recommend shifting from PD to hemodialysis in pregnancy, provided that good dialysis efficiency is reached. The only significant difference that emerges from the available evidence is a higher probability of having a small gestational age baby. The case mix of the mothers may, however, be different and data on PD efficiency are very scattered.

The elements in favor of continuing PD include better preservation of kidney function, lower risk of rapid fluid and electrolyte shifts, and avoidance of intermittent systemic anticoagulation. Furthermore, if the patients do not have dialysis access, the risks of creating an arteriovenous (AV) fistula or placing a tunneled dialysis catheter should be considered. The choice of the patient is listed here as the last point but should probably be the first, after critical and extensive counseling. While waiting for further studies, we believe that the choice of switching from PD to hemodialysis should be assessed on a case-by-case basis (Fig. 57.5).



• **Fig. 57.5** Pros and cons of switching from peritoneal dialysis to hemodialysis in pregnancy.

What we know:

Good pregnancy outcomes are reported on hemodialysis and PD.
The best results for pregnancy on dialysis are those reported with extended-hours daily hemodialysis.
The risk of small for gestational age babies may be higher on PD.
Most of the experts suggest choosing hemodialysis if dialysis start is needed in pregnancy.
There is no sound evidence supporting the systemic shift from PD to hemodialysis in pregnancy, provided that optimal dialysis efficiency is reached.

What we do not know:

The definition of adequate PD in pregnancy is not agreed upon, also in view of a possible shift to hemodialysis.

Dialysis Schedule on Peritoneal Dialysis in Pregnancy

As previously mentioned, there are fewer reports of PD compared to hemodialysis in pregnancy: conception rate is reported to be lower in PD patients, even if the ranges are wide. According to the ANZDATA Registry, conception on hemodialysis is approximately twice as likely as on PD.

Besides the lower dialysis efficiency, especially compared with extended-hours hemodialysis, this lower conception rate has been attributed to several factors, including the presence of hypertonic dialysate in the peritoneum, prior episodes of peritonitis, and the inability of the ovum to reach the Fallopian tubes.

Once pregnancy is started, PD is usually well tolerated; prescriptions should consider, especially in late pregnancy, abdominal fullness, with the possibility of catheter displacement, drain pain, dialysate flow disturbance, and in relation to the increased abdominal distension, a higher incidence of gastroesophageal reflux. Hemoperitoneum is rare, usually benign, and can be managed by increasing exchanges and using cooled dialysate. Severe hemoperitoneum that does not clear may be a sign of a pregnancy-related complication and should be managed in cooperation with the obstetrical team. The incidence of peritonitis is not reported as being increased.

The "ideal" type of PD (continuous ambulatory PD [CAPD] or automated PD [APD]) remains to be determined, and the choice needs to be individualized. In the absence of clear indications on the ideal urea level that needs to be maintained with this dialysis modality, some authors hold that the same target of predialysis urea levels of hemodialysis is reasonable (BUN of about 50 mg/dL), while others suggest that the patient should be stabilized at lower urea levels. Both choices are logical and sound (avoiding peaks or reaching a similar weekly clearance). The importance of residual kidney function is intuitive, suggesting monitoring it closely. In any case, dialysis prescriptions should be tailored to maximize efficiency, mainly by adjusting frequency and/or duration of dwells, as a general rule avoiding an increase in volumes and taking into account abdominal fullness, especially in the third trimester. In APD, tidal PD can be used in case of drain pain and to reduce gastroesophageal reflux. Tidal regimens may also alleviate catheter drain dysfunction; however, evidence is too scant to allow more detailed recommendations.

There is no absolute need for a cesarean section or a switch to hemodialysis in the case of cesarean section if this is performed extraperitoneally. However, only a few expert teams perform extraperitoneal cesarean sections; in these cases, PD can be resumed with small dwell volumes after 24 hours. Otherwise, a temporary switch to hemodialysis (1–3 weeks) should be carried out.

What we know:

Fertility is lower on PD than on hemodialysis.
Dialysis efficiency should be maximized in keeping with the indications on hemodialysis doses.
Tidal schedules may be preferred since they allow exchanges of lower volumes while ensuring high dialysis efficiency.

What we do not know:

Whether there is a difference between CAPD and APD in pregnancy and which modality should be preferred.
What the efficiency target on PD in pregnancy is.
What the best way to manage delivery in PD patients is.

Technical Aspects of Hemodialysis in Pregnancy

Frequency and Duration

Extended-hours daily hemodialysis is the dialysis treatment associated with the best results in pregnancy.

It is worth pointing out that the first systematic use of daily dialysis in pregnancy (on average 6 hours, 6 days per week) comes from the iconic center of Tassin, back in the 1980s and early 1990s when pregnant patients were switched to daily treatments (usually 6 hours) from the baseline schedule of 8 hours three times per week. These data were occasionally discussed but unfortunately never published, and we owe the first scientific reports of the results of extended daily dialysis in pregnancy to the Toronto investigators. Their results not only changed the way dialysis is managed in pregnancy but also affected the current concept of the adequacy of dialysis.

The Toronto experience provides clear data on the best dialysis schedule in pregnancy in patients without residual clearance; hemodialysis should be performed 8 hours per session, 6 or 7 days per week. Even before the data from Toronto became available, the dialysis dose was increased in pregnancy in most settings; thus, the Toronto experience set a new, very high standard, to which most experts are now complying, at least in settings in which dialysis is available without restrictions.

The results of pregnancy improve along with the increase in frequency of dialysis sessions, and once the daily frequency is reached, with dialysis duration, reaching statistical significance at or above 36 hours per week; the best results are, however, reported in few reference settings, Toronto ranking first, thus leaving open the question concerning how much is due to the presence of a skilled nephrology and obstetrician team defining a "system of care" and how much to dialysis per se.

The question remains open on whether shorter or less frequent dialysis may suffice in patients who have residual kidney function or small body size. Indeed, while the frequency of dialysis matters, the occasional reports obtained with short daily dialysis (2–3 hours) are not comparable with those of extended schedules, mainly with regard to a higher prevalence of prematurity.

Good outcomes with lower dialysis doses have been reported in settings like Mexico, in which the availability of dialysis is limited, and long extended dialysis is not feasible in most facilities. In such a context, a reasonable approach may be to perform daily dialysis sessions, whose duration is adapted to local means (the longer, the better).

Due to the rarity of pregnancy on dialysis and the limited availability of alternative treatments (hemofiltration, hemodiafiltration) worldwide, there is a lack of data on extracorporeal treatments other than bicarbonate dialysis. There are few reports on daily sessions of hemodiafiltration in pregnancy, suggesting that this technique may be equivalent to hemodialysis. The duration of the sessions was overall shorter, but the evidence is not sufficient to allow a sound comparison between hemodialysis and hemodiafiltration.

The dialysis schedules reported in the literature are different and often incomplete. We tried to summarize them into three main approaches, in Table 57.2: the first one is the reference approach, in keeping with the Toronto experience; the second one represents a sort of "minimum requirement" and is mainly derived from favorable experiences reported by low-resource settings; the third one tries to summarize the scattered experience with hemodiafiltration.

The use of Kt/V or urea levels for tailoring dialysis is not recommended in pregnancy, and as previously mentioned, a predialysis urea level below 100 mg/dL (BUN < 50 mg/dL) is commonly used as a surrogate marker of dialysis efficiency on the basis of the Canadian experience.

Bicarbonate levels in the dialysate should be carefully monitored due to the risk of inducing alkalosis and, as a starting point, should be reduced to 30–32 MEq/L; the concentration should be further adapted to blood levels.

Potassium levels should likewise be monitored due to the risk of depletion. On extended-hours daily dialysis, a concentration of 3.5 mEq/L should be the reference, again to be adapted to each patient. The issues regarding potential depletion of magnesium and phosphate are discussed in the following paragraphs (calcium–phosphate and dietary management).

What we know:

The best results are obtained with hemodialysis, 8 hours per day, 6 or 7 days per week.
Both frequency and duration of dialysis matter.
Predialysis urea is the most frequently employed marker of dialysis efficiency in pregnancy.
Bicarbonate should be lowered, and potassium increased in the dialysate.

What we do not know:

Whether hemodiafiltration offers an advantage with respect to hemodialysis.
Whether a wise combination of frequency and duration aimed at achieving target urea levels allows comparable results in settings where the daily extended-hours dialysis is not feasible.
What the role of integrated obstetric and nephrology care versus dialysis schedule in determining results is.

Dialysis Membranes

The most often employed terms are "high flux," "high permeability," and "biocompatible" membranes. However, there are no studies reporting on membrane size with respect to body size and the balance between depuration and loss of nutrients. Indeed, some nutrients may be dosed, such as albumin, vitamins, and phosphate, while others (trace elements,

TABLE 57.2 Examples of Dialysis Schedules for Pregnant Patients

Membrane	High flux	Low flux	High flux
Dialysis	Hemodialysis	Hemodialysis	Hemodiafiltration
Frequency	6–7 days	5–7 days/week	6–7 days
Duration	8 hours	4–8 hours	4–6 hours
Anticoagulation	Unfractionated heparin —low-molecular-weight heparin	Unfractionated heparin—low-molecular-weight heparin	Unfractionated heparin—low-molecular-weight heparin
Qb (mL/min)	250–300	200–300	250–300
Qd (mL/min)	500	300–500	500
K	3.5 MEq (to be adapted)	3.5 MEq (to be adapted)	3.5 MEq (to be adapted)
HCO_3	30–32 MEq (to be adapted)	30–32 MEq (to be adapted)	30–32 MEq (to be adapted)
Pros	Better removal of middle molecules with high flux membranes	Reduced loss of albumin and nutrients Less dependent on the quality of water May represent the only feasible option in some settings	Better removal of middle molecules Hemodynamic stability may be better
Cons	Higher albumin and nutrient loss Quality of water is fundamental	Reduced removal of middle molecules	Higher albumin and nutrient loss Cost may be higher; on-line HDF requires ultrapure water. Availability is limited

HDF, hemodiafiltration; Qb, blood flow; *Qd,* dialysate flow.

in particular) are not routinely dosed and may be consistently lost via highly permeable membranes, leading to the need for multiple supplementations. There are no data on the use of low-permeability membranes for reducing the loss of albumin and potentially important nutrients while keeping the same urea clearance and predialysis levels.

What we know:

Intensive dialysis is usually performed with high flux membranes, and the best results are obtained in this context.

During intensive dialysis, the loss of nutrients may be important with a need for supplementation of phosphate and water-soluble vitamins.

What we do not know:

Whether there is a difference in pregnancy results between attaining the same predialysis urea levels and high and low flux dialysis membranes.

What the loss of important nutrients is and how to control it in extended-hours dialysis.

Weight Management

Normal pregnancy is a hyperdynamic hyperhydrated state; this should be remembered when tailoring weight loss on dialysis. The usual markers of hydration on dialysis, i.e., blood pressure or muscle cramps, may be altered in pregnancy, the former by physiological vasodilation, the latter by the frequent occurrence of cramps in pregnancy, even in the absence of electrolyte derangements. None of the other means of establishing "dry weight," including bioimpedance or brain natriuretic peptide levels, have been validated in pregnancy and even less so in pregnancy on dialysis. Hence, we suggest tailoring the decision to the individual patient, taking into account the assessment tools that are available in each facility and the specific experience of the clinicians.

A weight gain of about 1 kg per month in the first and second trimester and up to 2 kg per month (500 g per week) in the third trimester of pregnancy is usually taken as a reference. However, this rule of thumb has to be adapted to each individual case and establishing the "dry weight" derives from an individualized assessment of diet, weight gain, dry weight, blood pressure, and utero-placental blood flows.

What we know:

Weight has to be adapted in pregnancy, balancing the risk of overhydration with the risk of critically reducing placental flow.

There is no clear algorithm to establish dry weight in on-dialysis pregnancy.

What we do not know:

How to define dry weight in on-dialysis pregnancy.

Anticoagulation and Antiplatelet Therapy

Antiplatelet therapy is now recommended in pregnancies at high risk of developing preeclampsia. However, no guidelines exist in this regard for on-dialysis pregnancy. In the context of immunologic diseases associated with hypercoagulability in pregnancy, the standard practice includes low-dose acetylsalicylic acid (usually 50 to 75 mg/day) in systemic lupus erythematosus (SLE) and in the presence of antiphospholipid antibodies without previous thrombotic events; heparin is added in case of obstetric antiphospholipid syndrome (APS) or history of thrombotic events. Unfractionated heparin is commonly used, but low-molecular-weight heparin has been shown to be safe and can also be used during the dialysis sessions.

The best heparin schedule in PD, on the off-dialysis day, or the need for extra administration in the off-dialysis hours needs to be established. Furthermore, on hemodialysis, the risk-to-benefit ratio of combining heparin and acetylsalicylic acid during dialysis has to be individually balanced with the bleeding risk. Conversely, in PD, we suggest prescribing low-dose acetylsalicylic acid at the start of pregnancy.

What we know:

Aspirin and heparin are not contraindicated in pregnancy.
Low-dose aspirin is now recommended for all pregnancies at high risk of preeclampsia.
Both unfractionated and low-molecular-weight heparin may be used during dialysis and for systemic anticoagulation.

What we do not know:

The advantages of antiplatelet and anticoagulant treatments in dialysis patients are not known.
The best schedule of heparin use for preventive anticoagulation has not been established.

Dialysis Access

Information on vascular access in pregnant women is scant.

Both fistula and tunneled catheters have drawbacks in pregnancy; rapid aneurysmal dilatation of the AV fistula in pregnancy has been reported; this complication may be more frequent in patients in whom the "ladder" policy or the (not recommended, but still used) "zone" cannulation is chosen. Conversely, the buttonhole technique and the tunneled catheter bear a risk of infection, which does not specifically increase in pregnancy but whose treatment may be particularly challenging due to the fact that the number of antibiotics that are considered safe in pregnancy is limited.

While the indication for a "fistula first" approach is sound, particularly in younger patients, in women already on dialysis with a well-functioning tunneled catheter, without frequent or recent infections, there is no evidence in favor of changing the vascular access type once pregnant.

On the other hand, several infectious complications were reported in the only large series reporting on complications of central venous catheters placed during pregnancy, albeit at a rate not unlike the one observed in the overall nonpregnant population.

Although pregnancy is generally considered a state of hypercoagulability, there is limited evidence that vascular access problems are more frequent in this context.

There are no specific data on which locking solutions should be preferred; no specific contraindications exist for heparin or citrate. Urokinase is not contraindicated in pregnancy, but there is no evidence favoring its use, and considering the possibility of developing neutralizing antibodies, there is no sound reason to recommend the use of urokinase-containing solutions in central venous catheters in pregnancy.

Daily hemodialysis has sometimes been associated with an increased rate of vascular access complications, be it an AV fistula or a graft, during or outside pregnancy. However, a difficult fistula may be very stressful for the patient, and the access choice should be carefully individualized.

In any case, the vascular access should be carefully and regularly checked in pregnancy, once more with an individualized policy.

What we know:

There is no specific complication related to central venous catheters in pregnancy on dialysis.
Even if the infectious risk is not increased, treatment of possible infections may be challenging.
A well-functioning AV fistula is not necessarily challenged by daily hemodialysis.
Rapid aneurysmal dilatation of a native fistula is occasionally reported in pregnancy.

What we do not know:

What the best locking solution for central venous catheters in pregnancy is.
What the best monitoring policy of an AV fistula or graft in pregnancy is.

Specific Support Therapies in Dialysis in Pregnancy

Anemia

Anemia is a frequent complication in pregnant dialysis patients. Maternal anemia has been correlated with preterm labor and fetal loss in a large series of nondialysis patients. Erythropoietin has been shown to be safe in pregnancy; its doses usually need to be increased by 50% to 100% in dialysis patients to achieve target hemoglobin levels of 10–11 g/dL during pregnancy.

The demand for iron, which is already an issue in healthy pregnant women, is likewise higher in pregnant women on dialysis. Losses in the dialysis circuit on daily hemodialysis may play a relevant role in iron deficiency.

Oral iron is safe in pregnancy, although it is often not sufficient to compensate for the increased needs; intravenous iron, targeted at transferrin saturation levels above 20%, has been given to pregnant dialysis patients without adverse events. However, in the later stages of pregnancy,

up to 80%–90% of parenteral iron may deposit in the fetus; therefore, it should be administered in small doses. Furthermore, intravenous iron has been associated with allergic reactions, which mostly occur within 24 hours of infusion and are usually self-limited but may rarely be life-threatening. While allergic reactions are reported with all intravenous preparations, they are less frequent with iron isomaltoside and iron carboxymaltose, which is the drug of choice wherever available. Ferric gluconate, instead, should be avoided due to the presence of benzyl alcohol and derivatives that may have fetal toxicity.

Folate and B_{12} should be monitored and supplemented in case of need, at doses adjusted upon blood levels. Folic acid is usually supplemented in women who plan a pregnancy since normal to high levels at conception is associated with a lower risk of spinal cord defects. However, levels may be low in unplanned pregnancies as folate is water-soluble and may be lost during high-efficiency dialysis sessions.

What we know:

The management of anemia in on-dialysis pregnancies usually requires higher doses of erythropoietin and iron.
Oral iron supplementation is safe but may be insufficient.
Iron isomaltoside should be preferred due to the lower risk of severe allergic reactions.
Folate and B_{12} supplementation are safe and may be needed in pregnancy.

What we do not know:

The target ferritin levels in on-dialysis pregnancies and the best treatment schedule, in particular in the last trimester.

Calcium–Phosphate Balance

In the overall population, the importance of having vitamin D levels within the normal range is increasingly acknowledged in pregnancy; in dialysis patients, vitamin D needs may be increased because of placental 25-hydroxyvitamin D3 conversion. In the absence of specific targets for women on dialysis, we suggest that vitamin D supplementation be guided by blood levels and calcium and phosphate balance.

Calcium supplements or calcium-based binders are safe; however, their use may not be needed if high dialysis efficiency is used, while sevelamer should not be used in pregnancy because animal studies suggest possible interference with fetal ossification, probably via reduced absorption of vitamin D. Indeed, phosphate levels are frequently low in patients on daily dialysis, and supplementation of phosphate, as well as of potassium or magnesium, may be needed. Magnesium is a powerful tocolytic, and we suggest checking it routinely to guide possible supplementation since low serum levels may facilitate or even induce uterine contractions.

To date, there are no studies that have examined the relationship between PTH levels and pregnancy outcomes; extended-hours daily hemodialysis usually improves the calcium-phosphate and PTH balance. In the nonuremic population, primary hyperparathyroidism is associated with a higher risk of pregnancy complications; the specific role of parathyroid hormone or of hypercalcemia is, however, difficult to disentangle. There is limited experience with the use calcimimetic agents; however, to date, their use has not been associated with adverse maternal-fetal events. The choice should be individualized, considering the lack of evidence.

What we know:

The need for vitamin D supplementation is higher in pregnancies on dialysis.
Phosphate control is not usually a problem on daily hemodialysis; however, phosphate supplementation may be needed.
Calcium-based phosphate binders may be used if needed.
Sevelamer is not advised on the basis of adverse effects in animal models.

What we do not know:

Whether the presence of hyperparathyroidism plays a role in pregnancy complications.
The safety of calcimimetic agents in pregnancy needs to be confirmed on a larger scale.

Nutritional Management in Dialysis in Pregnancy

The nutritional management of patients on dialysis in pregnancy is closely linked to the type of dialysis (hemodialysis or PD) and its schedule. Overall, there is consensus on the fact that energy and protein intake should be increased in pregnancy in women on dialysis, following a similar increase to what is recommended in the nonuremic population. The usually reported figures are between 1.2 and 1.5 g of protein per kg per day in pregnant women on dialysis; however, no studies have correlated protein intake with pregnancy outcomes. Furthermore, this advice is based upon the old nutritional indications on dialysis, determined when the definition of the "normal" protein intake was 1.2–1.0 g/kg/day, which has now been reduced to 0.8 g/kg/day. On these bases, in particular, if the woman suffers from nausea or hyperemesis, we recommend paying first of all attention to energy intake. An unbalanced diet in which most of the energy comes from protein intake may enhance hypercatabolism and worsen acidosis.

Intensifying dialysis increases the loss of nutrients, including albumin and amino acids. Indeed, the loss of albumin is strictly dependent upon the type of membrane used in hemodialysis (low or high flux). While the losses are usually considered clinically negligible when low-flow membranes are used, there are relevant differences ranging from about 1 to over 6 g per dialysis session when hemodialysis is performed with high flux membranes.

On PD, the increase in efficiency is also expected to increase nutrient losses, but the main differences depend upon the type of peritoneal transport.

Albumin is the best known of the nutrients that are lost on intensive dialysis, and it may be considered the marker of the loss of many other nutrients of small and medium molecular weight, including amino acids, water-soluble vitamins, and trace elements. Only some of them are routinely tested in dialysis patients, and there is little information on the actual needs in on-dialysis pregnancies.

The lack of appetite, gastrointestinal symptoms, and fatigue that are linked to long-hour dialysis may further complicate the picture. Supplementation with water-soluble vitamins is customary, and we recommend regularly dosing water-soluble vitamins, zinc, and copper and adjusting the supplementation on the basis of blood levels since, in some cases, as for example with vitamin C, both high and low levels may exert negative effects on the mother and/or the fetus.

The use of highly permeable high flux membranes, with albumin losses of over 3 g per session, should probably be discouraged, and the use of low-flux dialyzers may be considered in the presence of low albumin levels.

Foods that are rich in magnesium, potassium, and phosphate may be needed and, whenever possible, are preferable to adding oral supplements due to more physiological absorption and metabolism.

What we know:

Diet in pregnancy on dialysis should be unrestricted, with attention to providing sufficient amounts of proteins and calories.

Losses during dialysis may be relevant, especially for small-molecular-weight proteins, up to the albumin size, and hydrosoluble vitamins.

What we do not know:

What the protein and energy intake that best correlates with good pregnancy outcomes in dialysis patients is.

Which dialysis membranes should be used to allow optimal depuration without relevant albumin and nutrient losses.

Which vitamins and micronutrients should be routinely supplemented, and which ones have to be checked regularly.

Monitoring Policies

Pregnancy on dialysis is not only associated with several physiologic changes, whose modulation by dialysis is only partially known but is also usually associated with a relevant change in dialysis prescription; intensifying monitoring is therefore clinically sound. However, there are no available guidelines on how to monitor a pregnancy on dialysis. Very few papers report the frequency of check-ups, and the nonhomogeneity of policies for the management of chronic dialysis patients is enhanced.

In this context, the opinion of the Italian "best practices" is that intensification of dialysis requires an intensification of clinical and biochemical monitoring, which is usually linked to the dialysis session (creatinine, urea, electrolytes, complete blood cell count, acid-base balance, serum albumin) and should be performed at least twice monthly in stable patients. However, the frequency may be increased in specific patients and in facilities that have little experience with daily dialysis. Nutritional consultations are important and should be provided whenever possible, also taking into account the profound changes that are required from the usual, quite restrictive dietary policy (phosphate, potassium in particular) to an unrestricted one, especially on extended-hours hemodialysis. Obstetric and nephrology consultations should be combined to reduce stress on the patient.

Fetal monitoring is important, especially until the viability zone is reached. Monitoring is mainly aimed at timely detecting Doppler flow alterations and situations in which the risks to fetal health are higher if pregnancy is continued with respect to inducing delivery. According to the Italian best practice, fetal monitoring should be increased, and echographic examination should be performed every 1 to 2 weeks, paying particular attention to amniotic fluid quantity, or more frequently in case of complications, with serial monitoring of cervicometry. Doppler examination of the umbilical and uterine arteries should be performed every 1 to 3 weeks and more frequently in case of alterations.

On account of the differences in the monitoring policies of physiological and high-risk pregnancies, these have to be considered as mere suggestions to be adapted to the local policies, availability, and needs.

What we know:

Pregnancy on dialysis is associated with physiologic changes whose modulation by dialysis is only partially known and is usually associated with changes in prescriptions; the usual monitoring schedule of dialysis should be intensified.

Fetal monitoring should be aimed at evaluating amniotic fluid and fetal well-being and as an indication for delivery.

What we do not know:

We have no data comparing the frequency of monitoring or highlighting how it actually changes the pregnancy results.

Conclusions: Counseling Issues

Pregnancy may change the life of a woman on dialysis, who is often physically as well as psychologically vulnerable. While a positive outcome may be seen as confirmation that a woman on dialysis can attain the main life goals of a woman not on dialysis, a negative result may be devastating, in particular, if it occurs in the second half of the pregnancy (late miscarriages or intrauterine deaths) or if prematurity deeply affects the health of the newborn.

Prenatal counseling is a very delicate and culturally sensitive task, for which no general rule can be set. In the absence of precise quantification of risks and success rates, we usually employ the strategy of describing the best and the

worst scenarios, on the basis of the available data, emphasizing that the best scenario (healthy baby going home in mother's arms) is becoming increasingly frequent, but that the woman (or the family) has to be ready to cope with the worst ones (late miscarriage, intrauterine–neonatal death, or birth of a child with a severe handicap).

Having discussed the opposite scenarios, we usually touch on the points that are schematically summarized in Table 57.3, and we divide them into effects of pregnancy on the mother (including dialysis management) and effects of the mother's disease on the fetus. In such a context, we suggest stressing the degree of uncertainty that is present at all levels and the need for a deep commitment and reciprocal confidence between the multidisciplinary team and the patient.

In patients who want an opinion before pregnancy, we suggest that they should be informed that pregnancy outcomes are better after successful kidney transplantation than on dialysis. This information should be used to help them consider the decision of postponing conception until after

TABLE 57.3 Points Discussed in Counseling

Overall Points	Comments
Probability of success	The overall probability of success (baby going home in mother's arms) of a pregnancy on dialysis is above 80%, provided that compliance is good and treatment is intensified.
Reliability of previsions	Even if pregnancy is increasingly frequent in dialysis, it is still a rare event, and it is difficult to foresee all problems and the probability of success in every single case.
Need for commitment	Pregnancy on dialysis is a "full-time job" if one considers the need for intensive dialysis treatment and frequent check-ups, nutritional management, and regular therapies
Need for trust	In the absence of clear and reliable previsions, in a context in which each pregnancy is different and unique, reciprocal patient-physicians-team trust is the basis for such a demanding journey
Maternal Risks	**Comments**
Risk of death	Too low to be quantified; lack of long-term data to determine a carry-over effect of pregnancy
Risk of hyper immunization	No data specifically available; possible interference with kidney transplantation
Risk of hypertensive disorders of pregnancy	The risk seems high, but due to the lack of clear definition of hypertensive disorders of pregnancy in the context of dialysis, quantification is difficult.
Risk of other complications	This is a high-risk pregnancy and the risk of complications should be considered high; these include infectious ones (related or not to the vascular access or to peritoneal dialysis), bleeding (anticoagulation), or rare events such as dilatation of the arteriovenous fistula
Psychological risks	A negative outcome of pregnancy may have devastating effects on the patient and on the family; this should be borne in mind when starting pregnancy; psychological support may be indicated, although its acceptance is context sensitive.
Risks for the Baby	**Comments**
Risk of death	About 20% of the pregnancies end with a miscarriage, intrauterine death, or neonatal death. These risks are difficult to foresee at pregnancy start.
Risk of malformations	There is no increased risk of malformations with respect to the overall population (about 5% prevalence); of course, the risks linked to the baseline disease, if hereditary, or to the metabolic control of diabetes are not offset by dialysis.
Risk of prematurity and related complications	The main risks of prematurity are neurological and decrease progressively nearing term; cerebral hemorrhage is the most threatening complication, whose risk progressively drops after the 28th week. As reported in Fig. 57.2, minor developmental problems may be relatively common in "late preterm" babies. While these complications are frequent in dialysis patients, their frequency and severity do not appear to be different in children of on-dialysis mothers with respect to other premature babies.
Risk of other long-term complications	A growing body of evidence highlights the relationship between low birthweight, with or without prematurity or intrauterine growth restriction and risk of hypertension, metabolic syndrome, or CKD in adulthood. While these complications are frequent in dialysis patients, their frequency and severity does not appear to be different in children of on-dialysis mothers with respect to other premature babies.

CKD, Chronic kidney disease.

kidney transplant, at least in younger patients who have a higher probability of receiving a graft within a short time.

This information should be balanced by acknowledging that kidney function may not be fully normal after transplantation, that the current guidelines suggest waiting at least 1 year after transplantation, and that elective pregnancy should be carried out only in the absence of recent rejection episodes, with good kidney function, and ideally without hypertension or proteinuria. Furthermore, it should be acknowledged that the shortage of organs, the long waiting time, and the need for posttransplant stabilization may preclude pregnancy after transplantation in a woman in her late thirties or early forties.

As for dialysis management, we strongly suggest informing patients that a pregnancy on dialysis is a demanding task that can be seen as a "full-time job," and it requires not only dedicating more time to the dialysis session but also very good compliance to treatments and check-ups. Once more, we suggest mentioning the open issues and lack of guidelines, underlining the importance of reciprocal trust in undergoing this experience.

Recommended Reading

Pregnancy and renal disease. *Lancet.* 1975;2(7939):801–802.

A historic paper highlighting why traditionally pregnancy in advanced CKD were discouraged. Worth reading for contextualizing the different attitudes towards pregnancy in dialysis.

Abou-Jaoude P, Dubourg L, Bessenay L, et al. What about the renal function during childhood of children born from dialysed mothers? *Nephrol Dial Transplant.* 2012;27(6):2365–2369.

The first, and probably only study on kidney function of children from on dialysis mothers.

Attini R, Cabiddu G, Montersino B, et al. Contraception in chronic kidney disease: a best practice position statement by the Kidney and Pregnancy Group of the Italian Society of Nephrology. *J Nephrol.* 2020.

Recent and extensive guideline from a scientific society on birth control in women with CKD.

Attini R, Leone F, Parisi S, et al. Vegan-vegetarian low-protein supplemented diets in pregnant CKD patients: fifteen years of experience. *BMC Nephrol.* 2016;17(1):132.

The largest series reporting on dietary management in CKD pregnancy.

Attini R, Montersino B, Leone F, et al. Dialysis or a plant-based diet in advanced CKD in pregnancy? A case report and critical appraisal of the literature. *J Clin Med.* 2019;8(1).

A case study on diet or dialysis in pregnancy.

Cabiddu G, Castellino S, Gernone G, et al. Best practices on pregnancy on dialysis: the Italian Study Group on Kidney and Pregnancy. *J Nephrol.* 2015;28(3):279–288.

The first, and so-far only extensive guideline from a scientific society on pregnancy in women treated by dialysis.

Confortini P, Galanti G, Ancona G, et al. Full-term pregnancy and successful delivery in a patient on chronic hemodialysis. *Proc Eur Dial Transplant Assoc.* 1971;8:74–80.

The first historical report on pregnancy on dialysis.

Haase M, Morgera S, Bamberg C, et al. A systematic approach to managing pregnant dialysis patients–the importance of an intensified haemodiafiltration protocol. *Nephrol Dial Transplant.* 2005;20(11):2537–2542.

The largest series on pregnancy on HDF.

Hladunewich MA, Hou S, Odutayo A, et al. Intensive hemodialysis associates with improved pregnancy outcomes: a Canadian and United States cohort comparison. *J Am Soc Nephrol.* 2014;25(5):1103–1109.

One of the most important papers on pregnancy in dialysis patients. The pivotal paper demonstrating the advantages of intensive dialysis in pregnancy.

Jesudason S, Grace BS, McDonald SP. Pregnancy outcomes according to dialysis commencing before or after conception in women with ESRD. *Clin J Am Soc Nephrol.* 2014;9(1):143–149.

The largest registry study comparing outcomes according to dialysis start.

Mackenzie HS, Brenner BM. Fewer nephrons at birth: a missing link in the etiology of essential hypertension? *Am J Kidney Dis.* 1995;26(1):91–98.

The first version of the hypothesis of low nephron number and risk of hypertension and CKD.

Manisco G, Poti M, Maggiulli G, et al. Pregnancy in end-stage renal disease patients on dialysis: how to achieve a successful delivery. *Clin Kidney J.* 2015;8(3):293–299.

Case report and technical review of hemodialysis in pregnancy.

Oliverio AL, Bragg-Gresham JL, Admon LK, et al. Obstetric Deliveries in US Women With ESKD: 2002–2015. *Am J Kidney Dis.* 2020;75(5):762–771.

Recent paper reporting on the increase in pregnancies on dialysis and after kidney transplantation in the US.

Piccoli GB, Cabiddu G, Daidone G, et al. The children of dialysis: live-born babies from on-dialysis mothers in Italy—an epidemiological perspective comparing dialysis, kidney transplantation and the overall population. *Nephrol Dial Transplant.* 2014;29(8):1578–1586.

One of the two studies trying to allow a "graduation" of pregnancy probability on dialysis and after kidney transplantation (for the Australian study: Shahir 2013).

Piccoli GB, Minelli F, Versino E, et al. Pregnancy in dialysis patients in the new millennium: a systematic review and meta-regression analysis correlating dialysis schedules and pregnancy outcomes. *Nephrol Dial Transplant.* 2016;31(11):1915–1934.

The most recent systematic review on the results of pregnancy on dialysis in the new millennium.

Piccoli GB, Postorino V, Cabiddu G, et al. Children of a lesser god or miracles? An emotional and behavioural profile of children born to mothers on dialysis in Italy: a multicentre nationwide study 2000–12. *Nephrol Dial Transplant.* 2015;30(7):1193–1202.

One of the few studies analysing the outcome of the "children of dialysis".

Shah S, Christianson AL, Meganathan K, et al. Racial differences and factors associated with pregnancy in ESKD patients on dialysis in the United States. *J Am Soc Nephrol.* 2019;30(12):2437–2448.

A "must read" paper on the cultural interferences in getting pregnant while treated by dialysis in the US.

Shahir AK, Briggs N, Katsoulis J, et al. An observational outcomes study from 1966–2008, examining pregnancy and neonatal

outcomes from dialysed women using data from the ANZDATA Registry. *Nephrology (Carlton).* 2013;18(4):276–284.

One of the two studies trying to allow a "graduation" of pregnancy probability on dialysis and after kidney transplantation (for the Italian study: Piccoli 2014).

Tangren J, Nadel M, Hladunewich MA. Pregnancy and end-stage renal disease. *Blood Purif.* 2018;45(1–3):194–200.

Interesting updated review by the Toronto team.

Wiles K, Chappell L, Clark K, et al. Clinical practice guideline on pregnancy and renal disease. *BMC Nephrol.* 2019;20(1):401.

A clinical practice guidelines from the UK experts (contains some paragraphs on dialysis).

https://www.nice.org.uk/guidance/ng121/chapter/Recommendations#acute-kidney-injury-or-chronic-kidney-disease.

The only obstetric guideline with a (short) paragraph on CKD.

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Principles of Drug Usage in Dialysis Patients

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Introduction

The evolution of the field of dialysis and the advances in surgical procedures and access placement have made it possible to treat patients with end-stage kidney disease (ESKD) with dialysis therapy for more than 60 years. Improvements in pharmacotherapy management prior to and after dialysis initiation have contributed to these remarkable advancements. However, uremia may directly or indirectly affect different aspects of drug pharmacokinetics or pharmacodynamics. Most pharmacotherapeutic agents or their active/inactive metabolites are completely or partially eliminated by the kidneys.

The movement of drugs through different body compartments is known as pharmacokinetics, which defines drug absorption and bioavailability, tissue distribution, metabolism, and elimination. Patients with chronic kidney disease (CKD) have altered pharmacokinetic properties in addition to having a number of clinical comorbidities, which require close monitoring to avoid adverse drug reactions while correcting or preventing complications of these comorbid conditions. In patients with CKD, many aspects of pharmacokinetics, in particular drug elimination, are significantly different from those of patients with normal kidney function. For drugs that are excreted unchanged through the kidney, the dosage should be adjusted to avoid toxicities (Table 58.1). In addition, uremia may alter extrakidney drug metabolism. Depending on various factors (e.g., the size of the drug molecule and degree of protein binding), a significant amount of drug removal may occur during dialysis. To prevent toxicity and optimize efficacy, it is critical that these factors be taken into account and appropriate dosage adjustments made when prescribing drugs for dialysis patients. Finally, many pharmacotherapeutic and diagnostic agents, such as antimicrobial and iodinated contrast that are known nephrotoxins, make kidneys susceptible to future acute kidney injuries and consequently CKD. Discounting the intrinsic nephrotoxicity of these agents may predispose patients with early stages of kidney disease to develop late-stage CKD and eventually require dialysis. A number of studies have indicated that patients with CKD are prescribed drugs almost four times more than those without kidney disease. Additionally, exposure to potential nephrotoxins is significantly higher in this population.

This chapter discusses pharmacologic principles for prescribing drugs in CKD and provides a number of measures to reduce iatrogenic morbidities from drug dosing in this population. In addition, this chapter provides specific dosage recommendations for commonly used pharmacotherapeutic agents at different stages of kidney impairment for patients with CKD.

Pharmacologic Principles and Alterations in Uremia

Dosage modification in dialysis patients must take into account the effects of the uremic milieu on a variety of pharmacokinetic parameters, such as drug absorption, volume of distribution, protein binding, and drug metabolism. Bioavailability is defined as the percentage of administrated dose that reaches the systemic circulation. Drug bioavailability may be impaired because of delayed gastric emptying or edema of the gastrointestinal (GI) tract, particularly in diabetic patients with gastroparesis. Medications commonly prescribed in dialysis patients may alter drug bioavailability. For example, furosemide is used commonly in CKD patients, but bioavailability is reduced to less than 20% in this population. Gastric pH is frequently high because of the use of antacids or H_2 blockers, which may result in decreased absorption of medications requiring an acid milieu. Aluminum- or calcium-containing phosphate-binding antacids may form nonabsorbable chelation products with certain drugs, such as digoxin or tetracycline, with impairment of their absorption. Many oral antibiotics, such as fluoroquinolones, have decreased absorption when given in combination with multivalent metal cations such as iron or calcium carbonate/phosphate binders leading to therapeutic failure and requiring hospitalization in some patients.

TABLE 58.1 Nephrotoxins Based on Pathophysiologic Categories of Acute Renal Failure

1. Prerenal Failure
   NSAIDs, ACE inhibitors, cyclosporine, norepinephrine, angiotensin receptor blockers, diuretics, interleukins, cocaine, mitomycin C, tacrolimus, estrogen, quinine.
2. Acute Tubular Necrosis
   Antibiotics: aminoglycosides, cephaloridine, cephalothin, amphotericin B, rifampicin, vancomycin, foscarnet, pentamide.
   NSAIDs, glafenin, contrast media, acetaminophen, cyclosporine, cisplatin, IV immune globulin, dextran, maltose, sucrose, mannitol, heavy metals.
3. Acute Interstitial Nephritis
   Antibiotics: ciprofloxacin, methicillin, penicillin G, ampicillin, cephalothin, oxacillin, rifampicin.
   NSAIDs, glafenin, ADA, fenoprofen, naproxen, phenylbutazone, piroxacam, tolemetin, zomepirac, contrast media, sulfonamides, thiazides, phenytoin, furosemide, allopurinol, cimetidine, omeprazole, phenindione.
4. Tubular Obstruction
   Sulfonamides, methotrexate, methoxyflurane, glafenin, triamterene, ticrynafen, acyclovir, ethylene glycol, protease inhibitors
5. Hypersensitivity Angiitis
   Penicillin G, ampicillin, sulfonamides.
6. Thrombotic microangiopathy
   Mitomycin C, cyclosporine, oral contraceptives.

ACE, Angiotensin-converting enzyme; *ASA*, aspirin; *IV*, intravenous; *NSAIDs*, nonsteroidal anti-inflammatory drugs.

After drug absorption and equilibration, individual drugs distribute throughout the body in a characteristic manner. The apparent volume of distribution (V_d) is the quantity of drug in the body (L/kg body weight) divided by the plasma concentration at equilibrium. The scientific model of this relationship is the following equation:

$$C = \text{Dose} / V_d$$

V_d represents that amount of volume (in liters) in which the drug must have been dissolved to render the observed plasma concentration. Drug distribution is complex and can be influenced by protein binding, pKa, pH, tissue perfusion, and lipophilicity. Drugs that are highly tissue bound or lipid soluble usually have a large V_d, while drugs that are highly bound to circulating proteins are largely confined to the vascular space and therefore usually have a V_d of less than 0.2 L/kg. In a variety of disease states, including uremia and proteinuria, other drugs may alter the V_d of therapeutic agents. From a practical standpoint, the changes in V_d are usually not clinically significant except for those drugs that have a small V_d (< 0.7 L/kg) and are not highly protein bound under normal circumstances.

The degree of drug-protein binding is altered in uremic patients with potentially important pharmacologic consequences. The unbound or free drug is pharmacologically active and available for pharmacologic effects. Decreased binding of various drugs has been demonstrated in patients with kidney impairment. As a result, for any given drug level (bound plus unbound), the proportion of free or active drug is increased. The increased free drug concentrations may lead to an increased risk of drug toxicity. For example, patients with CKD and significant proteinuria are at a greater risk of phenytoin and procainamide toxicity. Although the plasma concentrations of these agents could be low, the elevated free fraction confers a risk of serious toxicity. Close follow-up and more frequent monitoring of serum concentrations are required to optimize clinical outcomes. For most drugs, because both drug elimination and pharmacologic activity are increased for any given dose, the clinical consequences are difficult to predict. Prescribing medications in patients with CKD requires a sophisticated understanding of the pharmacokinetic parameters of each agent.

When a medication reaches the systemic circulation, it is metabolized by the smooth endoplasmic reticulum in the liver, GI tract, and other tissues. Drug metabolism is a complex set of sequences that involves many organs and pathways in the body. The metabolism of a drug by the liver before entering the systemic circulation is known as *first-pass metabolism*. With first-pass metabolism, a drug is absorbed into the intestines and enters the portal vein before it reaches the liver for metabolism. After it is metabolized by the liver, the drug then enters the systemic circulation, where it produces an effect on the body. Generally, first-pass metabolism reduces the bioavailability of a given drug, thus decreasing the plasma concentration. In patients with CKD, the addition of phosphate binders, calcium, and iron may interfere with first-pass metabolism and reduce the drug exposure significantly.

In phase 1 metabolism, the oxidase class of enzymes is involved with drug metabolism. This oxidase group is more commonly known as CYP 450 enzymes. Oxidation metabolism leads to increased water solubility of most drugs. For all of this to occur, active CYP 450 enzymes are required. The most common CYP 450 enzyme is CYP 3A4, which metabolizes 50% of all drugs. With CYP 2D6, polymorphisms can affect the rate of drug metabolism. Uremia and kidney disease might affect expression of many of these enzymatic pathways.

With phase II metabolism, the enzymes involved with metabolism are transferases. The enzymes help transfer polar molecules to a drug to make them more soluble. Examples of these enzymes include glucuronate, glutathione, and nitration and sulfonation electrophilic aromatic substitution. The product of this reaction is known as a *conjugate*, thus the term "the conjugation reaction." One of the most well-known medications that use phase II metabolism is acetaminophen. The most common process for phase II metabolism is glucuronidation conjugation.

The kidneys are the most common route of drug excretion. The drug removal rate is typically expressed as elimination half-life (t½), the time required for the plasma concentration to decrease by 50%. The half-life is dependent on V_d and clearance (kidney, hepatic, or other) as expressed by the following formula:

$$t_{½} = 0.693 - \mu V_d / \text{clearance}$$

As the kidney clearance decreases, t½ will increase (assuming that V_d is unchanged). It should be noted that active drug metabolites may also be excreted by the kidney and therefore have a prolonged half-life in kidney failure.

Drug Administration

Drugs or their metabolites that are normally excreted by the kidney require dosage modification in advanced kidney failure. In general, the loading dose of a drug does not need to be changed unless the V_d is significantly altered. The maintenance regimen may be modified by the interval extension method or dosage reduction. The interval extension method uses the same dose at greater intervals and is useful for drugs with long half-lives. The dosage reduction method reduces the dosage and leaves the interval between doses unchanged. This method generally leads to more constant serum levels.

Monitoring drug levels can be very useful in guiding drug therapy and preventing toxicity. Interpretation of drug levels must be made in light of the amount of drug administered, the time elapsed since the last dose, and the route of administration.

After steady-state levels are reached, peak drug levels occur 30 to 60 minutes after parenteral administration or 1 to 2 hours after oral ingestion—and trough levels are drawn immediately before the next dose. In general, peak levels tend to correlate with drug efficacy, but trough levels are used as indicators of toxicity. Drug level monitoring can be expensive and is not always available. Drug level monitoring does not always reduce the incidence of toxicity. Ongoing clinical assessment is important even when drug levels are within the established therapeutic range. Most assays do not distinguish between free and protein-bound drugs in the plasma. An increase in unbound drugs is common in patients with kidney failure. Table 58.2 summarizes the therapeutic drug monitoring in kidney insufficiency for drugs where such monitoring is routinely recommended.

Kidney Function Assessment

Both blood urea nitrogen (BUN) and serum creatinine (Scr) are, at best, crude markers of kidney function. The glomerular filtration rate (GFR) is closely correlated with unchanged drug elimination through the kidney and is useful in determining dosage adjustments. For most drugs, the kidney is the major site for drug or a drug's metabolite elimination. The Cockcroft and Gault formula is the most commonly used method of calculating the creatinine clearance (CrCl), which has traditionally been used to approximate the GFR over last the 70 years. Although not the best marker for calculation of GFR, it is an excellent method to estimate kidney function and adjust drug dosing according to GFR. CrCl estimating methods are not valid in unstable patients during acute kidney injury or amputees, bodybuilders, and patients of extreme body habitus such as obesity or muscle wasting syndrome.

The Cockcroft and Gault formula (as follows) includes the variables of age (years), ideal body weight (IBW) (kg), and Scr (mg/dL) and calculates the CrCl (mL/min):

$$\text{CrCl} = (140 - \text{Age}) \times \text{IBW} / (\text{Scr} \times 72) (\times 0.85 \text{ for females})$$

Patients with acute kidney failure should have an assumed CrCl of less than 10 mL/min, and it should be remembered that CrCl overestimates the GFR. A new marker of GFR, iohexol, is currently being used in both the research and clinical settings to more accurately measure kidney function without exposing the patient to radiolabeled material. In addition, the Modification of Diet in Kidney Disease (MDRD) study, The CKD Epidemiology Collaboration (CKD-EPI), and cystatin C-derived equations are recently reported for estimating kidney function. These formulas approximate GFR rather than CrCl and, therefore, may be a more accurate estimate of kidney function. However, it is important to remember that all these equations are an estimation of GFR derived from specific populations and have not been validated in every group of patients. Each formula has some advantages and some limitations. Unsurprisingly, there is no ideal method to estimate GFR, and a one-size-fits-all approach does not apply in estimating GFR. All drug dosage adjustments should be considered in a full clinical context and potential drug toxicity.

The MDRD study equation is as follows.

$$\begin{aligned}\text{GFR}\left(\text{mL/min/1.73 m}^2\right) = {} & 175 \times (\text{Scr}) - 1.154 \times (\text{Age}) \\ & - 0.203 \times (0.742 \text{ if female}) \\ & \times (1.212 \text{ if African American})\end{aligned}$$

The CKD-EPI equation expressed as a single equation is as follows.

$$\begin{aligned}\text{eGFR} = {} & 142 \times \min(\text{standardized Scr} / \kappa, 1)^{\alpha} \\ & \times \max(\text{standardized Scr} / \kappa, 1) \\ & - 1.200 \times 0.9938^{\text{Age}} \times 1.012 \text{ [if female]}\end{aligned}$$

where:
Scr is serum creatinine in mg/dL,
κ is 0.7 for females and 0.9 for males,
α is −0.329 for females and −0.411 for males,
min indicates the minimum of Scr / κ or 1, and
max indicates the maximum of Scr / κ or 1.

TABLE 58.2 Therapeutic Drug Monitoring in Patients with Chronic Kidney Disease

Drug Name	Therapeutic Range	When to Draw Sample	How Often to Draw Levels
Aminoglycosides (conventional dosing) Gentamicin, tobramycin amikacin	Gentamicin and tobramycin: • Trough: 0.5–2 mg/L • Peak: 5–8 mg/L Amikacin: • Peak: 20–30 mg/L • Trough: < 10 mg/L 0.5–3 mg/L	• Trough: Immediately before dose • Peak: 30 minutes after a 30- to 45-minute infusion	• Check peak and trough with third dose. • For therapy less than 72 hours, levels not necessary. Repeat drug levels weekly or if renal function changes.
Aminoglycosides (24-hour dosing) Gentamicin, tobramycin, amikacin		Obtain random drug level 12 hours after dose	After initial dose. Repeat drug level in 1 week or if renal function changes.
Carbamazepine	4–12 μg/mL	Trough: Immediately before dosing	Check 2–4 days after the first dose or change in dose.
Cyclosporin	150–400 ng/mL	Trough: Immediately before dosing	Daily for first week, then weekly
Digoxin	0.8–2.0 ng/mL	12 h after maintenance dose	5–7 days after first dose for patients with normal renal and hepatic function; 15–20 days in anephric patients.
Lidocaine	1–5 μg/mL	8 hours after IV infusion started or changed	
Lithium	Acute: 0.8–1.2 mmol/L Chronic: 0.6–0.8 mmol/L	Trough: before AM dose at least 12 hours since last dose	
Phenobarbital	15–40 μg/mL	Trough: Immediately before dosing	Check 2 weeks after first dose or change in dose. Follow-up level in 1–2 months.
Phenytoin	10–20 μg/mL	Trough: Immediately before dosing	5–7 d after first dose or after change in dose.
Free Phenytoin	1–2 μg/mL		
Procainamide NAPA (*N*-acetyl procainamide), a procainamide metabolite	(A) 4–10 μg/mL • Trough: 4 μg/mL • Peak: 8 μg/mL (B) 10–30 μg/mL	(A) Trough: Immediately before next dose or 12–18 hours after starting or changing an infusion (B) Draw with procainamide sample	
Quinidine	1–5 μg/mL	Trough: Immediately before next dose	
Sirolimus	10–20 ng/dL	Trough: Immediately before next dose	
Tacrolimus (FK-506)	10–15 ng/mL	Trough: Immediately before next dose	Daily for first week, then weekly
Theophylline PO or aminophylline IV	15–20 μg/mL	Trough: Immediately before next dose	
Valproic acid	40–100 μg/mL	Trough: Immediately before next dose	Check 2–4 after first dose or change in dose
Vancomycin	• Trough: 5–15 mg/L • Peak: 25–40 mg/L	• Trough: Immediately before dose • Peak: 60 minutes after 60-minutes infusion	With third dose (when initially starting therapy or after each dosage adjustment). For therapy < 72 hours, levels not necessary. Repeat drug levels if renal function changes.

IV, Intravenous; *PO*, oral.

Effects of Dialysis on Drugs

Drug removal during dialysis is an important factor to consider when prescribing drug therapy for a patient with ESRD. A variety of factors affect dialysis drug clearance, including molecular weight, water solubility, degree of protein binding, and membrane clearance. Drugs with molecular weights of more than 500 daltons are poorly cleared by conventional hemodialysis (HD) membranes. In addition, drugs that are highly protein or tissue bound or highly lipid soluble are not dialyzed to a significant extent because of their large V_d. The clearance of some molecules of molecular weight of more than 500 daltons may be greater with peritoneal dialysis (PD) than with HD. From a practical standpoint, however, it is unusual for PD to remove drugs that are not also removed by HD.

The use of more permeable membranes, such as polysulfone, is becoming more the standard of care. Removal of drugs with relatively low molecular weights and small V_d could conceivably be enhanced with the use of these membranes. Vancomycin removal, for example, is significantly increased when polysulfone

TABLE 58.3 Antimicrobial Agents in Adult Patients with Chronic Kidney Disease

Drugs	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure: GFR >50 mL/min	GFR 10–50 mL/min	GFR <10 mL/min
Aminoglycoside Antibiotics					
Streptomycin	7.5 mg/kg q12h (1.0 g q24h for tuberculosis)	60%	q24h	q24–72h	q72–96h
Kanamycin	7.5 mg/kg q8h	50%–90%	60%–90% q12h or 100% q12–24h	30%–70% q12–18h or 100% q24–48h	20%–30% q24–48h or 100% q48–72h
Gentamicin	1.7 mg/kg q8h	95%	60%–90% q8–12h or 100% q12–24h	30%–70% q12h or 100% q24–48h	20%–30% q24–48h or 100% q48–72h
Tobramycin	1.7 mg/kg q8h	95%	60%–90% q8–12h or 100% q12–24h	30%–70% q12h or 100% q24–48h	20%–30% q24–48h or 100% q48–72h
Netilmicin	2 mg/kg q8h	95%	50%–90% q8–12h or 100% q12–24h	20%–60% q12h or 100% q24–48h	10% to 20% q24–48h or 100% q48 to 72
Amikacin	7.5 mg/kg q12h	95%	60% to 90% q12h or 100% q12 to 24h	30% to 70% q12 to 18h or 100% q24–48h	20% to 30% q24–48h or 100% q48 to 72h
Cephalosporin					
Cefdinir	300 mg PO BID or 600 mg PO QD	~15%–20%	No renal adjustment	CrCl <30 mL/min: oral: 300 mg once daily	
Cefaclor	250–500 mg q8h	70%	100%	100%	50%
Cefadroxil	500–1 g q12h	80%	100%	100%	50%
Cefixime	200–400 mg q12h	85%	100%	100%	50%
Cefpodoxime	200 mg q12h	30%	100%	100%	100%
Ceftibuten	400 mg q24h	70%	100%	100%	50%

membranes are used compared with cuprophane membranes. Thus, supplemental vancomycin administration is required after each dialysis session with a polysulfone membrane to maintain therapeutic vancomycin levels.

Continuous hemofiltration modalities (i.e., continuous kidney replacement therapy) are gaining popularity in intensive care units for the management of patients with acute kidney injury. In this procedure, convective mass transfer removes solutes and drugs. In general, a drug is significantly removed if it is primarily distributed in the plasma water and is not highly protein bound. Measurement of serum drug levels may be helpful in guiding the need for supplemental dosing with these modalities. For most drugs with limited toxicities, the full dose should be given with minor dosage adjustments.

Dosing Tables

Table 58.3 presents key information required for prescribing medications in dialysis patients. Table 58.3 provides

Comments	HD	CAPD	Continuous Venovenous Hemofiltration
Nephrotoxic, ototoxic; toxicity worse when hyperbilirubinemic; measure serum levels for efficacy and toxicity Peritoneal absorption increases with presence of inflammation V_d increases with edema, obesity, and ascites			
For the treatment of TB; may be less nephrotoxic than other members of class	1/2 normal dose after dialysis	20–40 mg/L/day	Dose for GFR 10–50 mL/min and measure levels
Do not use once-daily dosing in patients with CrCl < 30–40 mL/min or in patients with ARF or uncertain level of kidney function	1/2 full dose after dialysis	15–20 mg/L/day	Dose for GFR 10–50 mL/min and measure levels
	1/2 full dose after dialysis	3–4 mg/L/day	Dose for GFR 10–50 mL/min and measure levels
	1/2 full dose after dialysis	3–4 mg/L/day	Dose for GFR 10–50 mL/min and measure levels
May be less ototoxic than other members of class Peak: 6–8 and trough: < 2	1/2 full dose after dialysis	3 to 4 mg/L/day	Dose for GFR 10 to 50 mL/min and measure levels
Monitor levels; ototoxicity, nephrotoxicity; avoid use with potent diuretics Peak: 20–30 and trough: < 5	1/2 full dose after dialysis	15 to 20 mg/L/day	Dose for GFR 10 mg/L to 50 mL/min and measure levels
Coagulation abnormalities, transitory elevation of BUN, rash, and serum sickness–like syndrome			
Administer 2 hours before or after antacids or iron supplements; may turn stool reddish in color	Initial 300 mg QOD and 300 mg after dialysis		
	250 mg BID after dialysis	250 mg q8–12h	N/A
	0.5 to 1.0 g after dialysis	0.5 g/day	N/A
	300 mg after dialysis	200 mg/day	Not recommended
	200 mg after dialysis	Dose for GFR < 10 mL/min	N/A
	300 mg after dialysis	No data: dose for GFR < 10 mL/min	Dose for GFR 10–50 mL/min

Continued

TABLE 58.3 Antimicrobial Agents in Adult Patients with Chronic Kidney Disease—cont'd

Drugs	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure		
			GFR >50 mL/min	GFR 10–50 mL/min	GFR <10 mL/min
Cefuroxime axetil	250–500 mg q8 h	90%	100%	100%	100%
Cephalexin	250–500 mg q8 h	95%	100%	100%	100%
Cephradine	250–500 mg q8 h	100%	100%	100%	50%
Cefazolin	1–2 g IV q8h	80%	q8h	q12h	q12–24h
Cefepime	1–2 g IV q8h	85%	q8–12h	q12h	q24h
Cefmetazole	1–2 g IV q8h	85%	q8h	q12h	q24h
Cefoperazone	1–2 g IV q12h	20%	No renal adjustment is required		
Cefotaxime	1–2 g IV q6–8h	60%	q8h	q12h	q12–24h
Cefotetan	1–2 g IV q12h	75%	q12h	q12–24h	q24h
Cefoxitin	1–2 g IV q6h	80%	q6h	q8–12h	q12h
Ceftazidime	1–2 g IV q8h	70%	q8h	q12h	q24h
Ceftriaxone	1–2 g IV q24h	50%	No renal adjustment is required		
Cefuroxime sodium	0.75–1.5 g IV q8h	90%	q8h	q8–12h	q12–24h
Penicillins					
Amoxicillin	500 mg PO q8h	60%	100%	100%	50%–75%
Ampicillin	500 mg PO q6h	60%	100%	100%	50%–75%
Dicloxacillin	250–500 mg PO q6h	50%	100%	100%	50%–75%
Penicillin V	250–500 mg PO q6h	70%	100%	100%	50%–75%
Ampicillin	1–2 g IV q6h	60%	q6h	q8h	q12h
Nafcillin	1–2 g IV q4h	35%	No renal adjustment is required		
Penicillin G	2–3 million units IV q4h	70%	q4–6h	q6h	q8h
Piperacillin	3–4 g IV q4–6h		No renal adjustment is required		
Ticarcillin–clavulanate	3.1 g IV q4–6h	85%	1–2 g q4h	1–2 g q8h	1–2 g q12h
Piperacillin–tazobactam	3.375 g IV q6–8h	75%–90%	q4–6h	q6–8h	q8h

Comments	HD	CAPD	Continuous Venovenous Hemofiltration
Malabsorbed in the presence of H_2 blockers; absorbed better with food	Dose after dialysis	Dose for GFR <10 mL/min	N/A
Rare allergic interstitial nephritis; absorbed well when given intraperitoneally; may cause bleeding from impaired prothrombin biosynthesis	Dose after dialysis	Dose for GFR <10 mL/min	N/A
	Dose after dialysis	Dose for GFR <10 mL/min	N/A
	0.5–1.0 g after dialysis	0.5 g q12h	Dose for GFR 10–50 mL/min
	1 g after dialysis	Dose for GFR <10 mL/min	Not recommended
	Dose after dialysis	Dose for GFR <10 mL/min	Dose for GFR 10–50 mL/min
Displaced from protein by bilirubin; reduce dose by 50% for jaundice; may prolong PT	1 g after dialysis	None	None
	1 g after dialysis	1 g/day	1 g q12h
	1 g after dialysis	1 g/day	750 mg q12h
May produce a false increase in serum creatinine by interference with assay	1 g after dialysis	1 g/day	Dose for GFR 10–50 mL/min
	1 g after dialysis	0.5 g/day	Dose for GFR 10–50 mL/min
	Dose after dialysis	750 mg q12h	Dose for GFR 10–50 mL/min
	Dose after dialysis	Dose for GFR <10 mL/min	1.0 g q12h
Bleeding abnormalities, hypersensitivity, seizures			
	Dose after dialysis	250 mg q12h	N/A
	Dose after dialysis	250 mg q12h	Dose for GFR 10–50 mL/min
	None	None	N/A
Taken preferably on an empty stomach to increase oral absorption (1 hour before or 2 hours after meals)	Dose after dialysis	Dose for GFR <10 mL/min	N/A
	Dose after dialysis	250 mg q12h	Dose for GFR 10–50 mL/min
	None	None	Dose for GFR 10–50 mL/min
	Dose after dialysis	Dose for GFR <10 mL/min	Dose for GFR 10–50 mL/min
Sodium, 1.9 mEq/g	Dose after dialysis	Dose for GFR <10 mL/min	Dose for GFR 10–50 mL/min
Sodium, 5.2 mEq/g	3.0 g after dialysis	Dose for GFR <10 mL/min	Dose for GFR 10–50 mL/min
Sodium, 1.9 mEq/g	Dose after dialysis	Dose for GFR <10 mL/min	Dose for GFR 10–50 mL/min

Continued

TABLE 58.3 Antimicrobial Agents in Adult Patients with Chronic Kidney Disease—cont'd

Drugs	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure		
			GFR >50 mL/min	GFR 10–50 mL/min	GFR <10 mL/min
Quinolones					
Ciprofloxacin	200–400 mg IV q24h	60%	q12h	q12–24h	q24h
Levofloxacin	500 mg PO q24h	70%	q12h	250 q12h	250 q12h
Moxifloxacin	400 mg q24h	20%	No renal adjustment is required		
Nalidixic acid	1.0 g q6h	High	100%	Avoid	Avoid
Norfloxacin	400 mg PO q12h	30%	q12h	q12–24h	q24h
Ofloxacin	200–400 mg PO q12h	70%	q12h	q12–24h	q24h
Doxycycline	50–100 mg PO q12h	40%	No renal adjustment is required		
Minocycline	200 mg ×1 PO then 100 mg PO q12h	20%	Do not exceed 200 mg IR in 24 hours for GFR <80 mL/min		
Tigecycline	100 mg IV once then 50 mg IV q12h	33%	No renal adjustment is required		
Azithromycin	250–500 mg PO q24h	6%	No renal adjustment is required		
Aztreonam	1–2 g IV q8–12h	60%–70%	None	1–2 g ×1 dose, then 50%	1–2 g ×1 dose, then 25%
Clarithromycin	500 mg PO q12h		No renal adjustment is required		
Clindamycin	150–450 mg PO q8h	10%	No renal adjustment is required		
Dirithromycin	500 mg PO q24h		No renal adjustment is required		
Erythromycin	250–500 mg PO q6h	15%	No renal adjustment is required		
Ertapenem	1 g IV q24h		1 g IV q24h	0.5 g IV q24h	0.5 g IV q24h
Imipenem–cilastatin	250–500 mg IV q6h	50%	500 mg q8h	250–500 q8 to 12h	250 mg q12h

Comments	HD	CAPD	Continuous Venovenous Hemofiltration
Food, dairy products, tube feeding, and $Al(OH)_3$ may decrease the absorption of quinolones			
Poorly absorbed with antacids, sucralfate, and phosphate binders; IV dose one-third of oral dose; decreases phenytoin levels	250 mg q12h (200 mg if IV)	250 mg q8h (200 mg if IV)	200 mg IV q12h
L-isomer of ofloxacin: appears to have similar pharmacokinetics and toxicities	Dose for GFR < 10 mL/min	Dose for GFR < 10 mL/min	Dose for GFR 10–50 mL/min
Poorly absorbed with antacids, sucralfate, and phosphate binders; sun sensitivity, QT prolongation, tendon rupture	No data	No data	No data
Agents in this group are malabsorbed in the presence of magnesium, calcium, aluminum, and iron; theophylline metabolism is impaired; higher oral doses may be needed to treat CAPD peritonitis	Avoid	Avoid	N/A
See above	Dose for GFR < 10 mL/min	Dose for GFR < 10 mL/min	N/A
See earlier	100–200 mg after dialysis	Dose for GFR < 10 mL/min	300 mg/day
Not dialyzable	None	None	None
Consider decreasing dosing interval for ER formulations in GFR < 80 mL/min	No data	No data	No data
Poorly dialyzed. Generally bacteriostatic. Active against MRSA	None	None	None
No drug–drug interaction with CSA/KF; Oral suspension (extended release) should be taken on empty stomach: at least 1 hour before or 2 hours following a meal	None	None	None
Administered IV or IM. Maximum 8 g per 24 hours. Safe in PCN allergy	1–2 g × 1, then 25%	1–2 g × 1, then 25%	2 g × 1, then 1–2 g q12h
Can cause metallic taste; XL formulation should be taken with food and not crushed	None	None	None
Increase CSA/FK level; can cause CDAD; oral—administer with full glass of water to minimize esophageal ulceration	None	None	None
Nonenzymatically hydrolyzed to active compound erythromycylamine	None	No data: none	Dose for GFR 10–50 mL/min
Increase CSA/FK level; avoid in transplant patients	None	None	None
	Dose after dialysis	Dose for GFR < 10 mL/min	Dose for GFR < 30
Seizures in ESRD; nonrenal clearance in ARF is less than in chronic renal failure; administered with cilastatin to prevent nephrotoxicity of renal metabolite	Dose after dialysis	Dose for GFR < 10 mL/min	Dose for GFR 10–50 mL/min

Continued

TABLE 58.3 Antimicrobial Agents in Adult Patients with Chronic Kidney Disease—cont'd

Drugs	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure		
			GFR >50 mL/min	GFR 10–50 mL/min	GFR <10 mL/min
Meropenem	1 g IV q8h	65%	1 g q8h	0.5–1 g q12h	0.5–1 g q24h
Metronidazole	500 mg IV q6h	20%	No renal adjustment is required		
Nitrofurantoin (Macrodantin)	50–100 mg PO QID	40%	None for GFR >60 mL/min	Use in GFR <60 mL/min is contraindicated per package label. However, short-term use is likely safe for uncomplicated acute cystitis	
Nitrofurantoin	100 mg PO q12h				
Pentamidine	4 mg/kg/day	5%	q24h	q24h	q48h
Trimethoprim/ sulfamethoxazole	800/160 mg PO q12h	70%	q12h	q18h	q24h
Vancomycin	1 g IV q12h	90%	q12h	q24–36h	q48–72h
Vancomycin	125–250 mg PO q6h	0%	100%	100%	100%
Dalbavancin	1500 mg IV ×1 **OR** 1000 mg IV ×1 then 500 mg IV 1 week later	33%	None	GFR <30: 1125 mg IV once **OR** 750 mg IV once + 375 mg IV 1 week later	
Oritavancin	1200 mg IV once	5%	None	Not studied in GFR <30	
Daptomycin	4–10 mg/kg IV q24h	78%%	None	GFR <30: 4–6 mg/kg q48h	
Linezolid	600 mg PO q12h	~30%	No renal adjustment required		
Rifampin (RIF)	300–600 mg PO q24h	20%	No renal adjustment is required		
Rifapentine (RPT)	5 mg/kg MAX: 300 mg PO QD	21%–30%	100%	50%–100%	50%–100%
Isoniazid (INH)	(5 mg/kg) MAX: 300 mg PO or IM QD	75%–95%	No renal adjustment is required		
Pyrazinamde (PZA)	1000 mg PO QD	70%	None	25–35 mg/kg three times a week	25–35 mg/kg three times a week

Comments	HD	CAPD	Continuous Venovenous Hemofiltration
Fewer seizures than with imipenem	Dose after dialysis	Dose for GFR < 10 mL/min	Dose for GFR 10–50 mL/min
Peripheral neuropathy, increase LFTs, disulfiram reaction with alcoholic beverages (avoid alcohol during and 3 days after), might cause urine to turn reddish or brown, take on empty stomach (especially ER dose) unless GI upset then take with food	Dose after dialysis	Dose for GFR < 10 mL/min	Dose for GFR 10–50 mL/min
Monohydrate/macrocrystal formulation	Contraindicated	Contraindicated	Contraindicated
Macrocrystal only formulation			
Inhalation may cause bronchospasm; IV administration may cause hypotension, hypoglycemia, and nephrotoxicity	None	None	None
Increase serum creatinine; can cause hyperkalemia; increased fluid intake should be maintained to prevent crystalluria and stone; photosensitivity	Dose after dialysis	q24h	q18h
Nephrotoxic, ototoxic; may prolong the neuromuscular blockade effect of muscle relaxants, peak: 30–40, trough: 5–10	500 mg q12–24 h (high FLX)	1.0 g q24–96h	500 mg q12h
Oral vancomycin is indicated only for the treatment of *Clostridium difficile*	100%	100%	100%
Long-acting antibiotic used for SSTI. Bactericidal against *Staphylococcus aureus* and *Streptococcus pyogenes*	None	None	No data
Long-acting antibiotic used for SSTI. Bactericidal	None	No data	No data
Never use for pneumonia because the drug is inactivated by pulmonary surfactant. Bactericidal in concentration dependent manner	Dose for GFR < 30 after HD on dialysis days	Dose for GFR < 30	8 mg/kg q48h
Avoid tyramine products. Oral suspension should be gently mixed. Do not shake.	Dose after dialysis	600 mg/day in 1 to 2 divided doses	
Decrease CSA/FK level; many drug interactions	None	Dose for GFR < 10 mL/min	Dose for GFR < 10 mL/min
	50%–100% of dose, no supplementation	50%–100% plus an extra 50%–100% after PD	
Hepatotoxicity	None	None	
Gout	25–35 mg/kg three times a week after HD, supplement if next dose not right after	None	

Continued

TABLE 58.3 Antimicrobial Agents in Adult Patients with Chronic Kidney Disease—cont'd

Drugs	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure		
			GFR >50 mL/min	GFR 10–50 mL/min	GFR <10 mL/min
Ethambutol (EMB)	800–1600 mg PO QD (weight based)	80%	None	15–25 mg/kg three times a week	15–25 mg/kg three times a week
Cycloserine	10–15 mg/kg/day PO, QD or BID	60%–70%	None	500 mg three times a week OR 250 mg QD	Contraindicated (per package insert)
Capreomycin	10–15 mg/kg IM or IV five to seven times a week MAX: 1 g/dose	52%	None	Two to three times a week	Two to three times a week
Aminosalicylic acid	4 g PO BID-TID	80%	None	4 g PO BID	Contraindicated (per package insert)
Ethionamide	15–20 mg/kg/day PO, QD, or BID	100%	None	250–500 mg QD	250–500 mg QD
Bedaquiline	400 mg PO QD two times a week, then 200 mg PO three times a week	<0.001%	None	None	Not defined
Pretomanid	200 mg PO QD	50%	No renal dose adjustment		
Amphotericin B	0.5 mg–1.5 mg/kg/day	<1%	No renal adjustment is required		
Amphotec	4–6 mg/kg/day	<1%	No renal adjustment is required		
Abelcet	5 mg/kg/day	<1%	No renal adjustment is required		
AmBisome	3–5 mg/kg/day	<1%	No renal adjustment is required		
Azoles and Other Antifungals					
Fluconazole	200–800 mg IV q24h/q12h	70%	100%	100%	50%
Flucytosine	37.5 mg/kg	90%	q12h	q16h	q24h
Griseofulvin	125–250 mg q6h	1%	100%	100%	100%
Itraconazole	200 mg q12h	35%	100%	100%	50%
Ketoconazole	200–400 mg PO q24h	15%	100%	100%	100%
Miconazole	1200–3600 mg/day	1%	100%	100%	100%
Posaconazole	200 mg q6h	1%	100%	100%	100%
Terbinafine	250 mg PO q24h	>1%	100%	100%	100%

Comments	HD	CAPD	Continuous Venovenous Hemofiltration
Optic neuropathy	15–25 mg/kg three times a week. No supplement	15–25 mg/kg three times a week. No supplement	
Neuropathy	500 mg three times a week after HD, supplement if next dose not right after	Not defined	
	Two to three times a week after dialysis, consider supplement if next dose not right after	Not defined	
	4 g PO BID	Not defined	
	250–500 mg QD, after dialysis, no supplement	Not defined	
	Not defined	Not defined	
	None	None	None
Nephrotoxic; infusion-related reactions; give 250 cc NS before each dose	q24h	q24h	q24–36h
	q24h	q24h	q24–36h
	q24h	q24h	q24–36h
	q24h	q24h	q24–36h
Increase CSA/FK level			
QT prolongation with high dose (avoid use with terfenadine)	200 mg after dialysis	Dose for GFR < 10 mL/min	Dose for GFR 10–50 mL/min
Hepatic dysfunction; marrow suppression more common in azotemic patients	Dose after dialysis	0.5–1.0 g/day	Dose for GFR 10–50 mL/min
	None	None	None
Poor oral absorption	100 mg q12–24h	100 mg q12–24h	100 mg q12–24h
Hepatotoxic; requires acid to be absorbed so avoid antacid 2 hours before and after dose, significant cyp450 DDI	None	None	None
	None	None	None
	100%	100%	100%
	100%	100%	100%

Continued

TABLE 58.3 Antimicrobial Agents in Adult Patients with Chronic Kidney Disease—cont'd

Drugs	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure		
			GFR >50 mL/min	GFR 10–50 mL/min	GFR <10 mL/min
Voriconazole	4–6 mg/kg q12h	1%	100%	100%	100%
Caspofungin	70 mg LD; then 50 mg/day	1%	100%	100%	100%
Micafungin	100–150 mg IV daily	1%	100%	100%	100%
Anidulafungin	200 mg LD; then 100 mg/day	1%	100%	100%	100%
Acyclovir	200–800 mg PO five times a day	50%	100%	100%	50%
Adefovir	10 mg q24h	45%	100%	10 mg q48h	10 mg q72h
Amantadine	100–200 mg q12h	90%	100%	50%	q96h–7 days
Cidofovir	5 mg/kg weekly ×2 (induction); 5 mg/kg every 2 weeks	90%	Avoid in CKD	No data: avoid	No data: avoid
Delavirdine	400 mg q8h	5%	No data: 100%	No data: 100%	No data: 100%
Didanosine	200 mg q12h (125 mg if <60 kg)	40%–69%	q12h	q24h	50% q24h
Emtricitabine	200 mg q24h	86%	q24h	q48–72h	q96h
Entecavir	0.5 mg q24h	62%	q24h	q48–72h	q96h
Famciclovir	250–500 mg PO q8h–q12h	60%	q8h	q12h	q24h
Foscarnet	40–80 mg IV q8h	85%	40–20 mg q8–24h according to CrCl		
Ganciclovir IV	5 mg/kg q12h	95%	q12h	q24h	2.5 mg/kg q24h
Ganciclovir	1000 mg PO q8h	95%	1000 mg q8h	1000 mg q12h	1000 mg q24h
Indinavir	800 mg q8h	10%	No data: 100%	No data: 100%	No data: 100%
Lamivudine	150 mg PO q12h	80%	q12h	q24h	50 mg q24h
Maraviroc	300 mg q12h	20%	300 mg q12h	No data	No data
Nelfinavir	750 mg q8h	No data	No data	No data	No data
Nevirapine	200 mg q24h × 14 days	<3	No data: 100%	No data: 100%	No data: 100%
Oseltamivir	75 mg q12h	99%	75 q12h	75 mg/day	75 mg q48h

Comments	HD	CAPD	Continuous Venovenous Hemofiltration
Avoid IV formulation in CKD	100%	100%	100%
	100%	100%	100%
	100%	100%	100%
	None	None	None
Poor absorption; neurotoxicity in ESRD; IV preparation can cause renal failure if injected rapidly (infused over 1 hour), check for phlebitis and rotate infusion sites	Dose after dialysis	Dose for GFR < 10 mL/min	3.5 mg/kg/day
Renal toxicity	10 mg weekly after HD	No data	No data
	None	None	Dose for GFR 10–50 mL/min
Dose-limiting nephrotoxicity with proteinuria, glycosuria, renal insufficiency; nephrotoxicity and renal clearance reduced with coadministration of probenecid	No data	No data	Avoid
	No data	No data	No data: dose for GFR 10–50 mL/min
Pancreatitis	Dose after dialysis	Dose for GFR < 10 mL/min	Dose for GFR < 10 mL/min
		Dose after dialysis	No data
		Dose after dialysis	No data
VZV: 500 mg PO q8h HSV: 250 PO q12h Metabolized to active compound penciclovir	Dose after dialysis	No data	No data: dose for GFR 10–50 mL/min
Nephrotoxic, neurotoxic, hypocalcemia, hypophosphatemia, hypomagnesemia, and hypokalemia	Dose after dialysis	Dose for GFR < 10 mL/min	Dose for GFR 10–50 mL/min
Granulocytopenia and thrombocytopenia	Dose after dialysis	Dose for GFR < 10 mL/min	2.5 mg/kg q24h
Oral ganciclovir should be used ONLY for prevention of CMV infection; always use IV ganciclovir for the treatment of CMV infection	No data: dose after dialysis	No data: dose for GFR < 10 mL/min	N/A
Nephrolithiasis; ARF due to crystalluria, tubulointerstitial nephritis	No data	No data: dose for GFR < 10 mL/min	No data
For hepatitis B	Dose after dialysis	No data: dose for GFR < 10 mL/min	Dose for GFR 10–50 mL/min
Drug interaction with CYP III-A	No data	No data	No data
	No data	No data	No data
May be partially cleared by HD and PD	Dose after dialysis	No data: dose for GFR < 10 mL/min	No data: dose for GFR 10–50 mL/min
	Dose after dialysis		

Continued

TABLE 58.3 Antimicrobial Agents in Adult Patients with Chronic Kidney Disease—cont'd

Drugs	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure: GFR >50 mL/min	GFR 10–50 mL/min	GFR <10 mL/min
Ribavirin	500–600 mg q12h	30%	100%	100%	50%
Rifabutin	300 mg q24h	5%–10%	100%	100%	100%
Rimantadine	100 mg PO q12h	25%	100%	100%	50%
Ritonavir	600 mg q12h	3.50%	No data: 100%	No data: 100%	No data: 100%
Saquinavir	600 mg q8h	<4%	No data: 100%	No data: 100%	No data: 100%
Stavudine	30–40 mg q12h	35%–40%	100%	50% q12–24h	50% q24h
Telbivudine	600 mg PO daily		100%	600 mg q48h	600 mg q96h
Tenofovir	300 mg q24h		100%	300 mg q48–72h	300 mg q96h
Valacyclovir	500–1000 mg q8h	50%	100%	50%	25%
Valganciclovir	900 mg PO daily or q12h		100%	50%	25%
Vidarabine	15 mg/kg infusion q24h	50%	100%	100%	75%
Zanamivir	2 puffs q12h × 5 days	1%	100%	100%	100%
Zalcitabine	0.75 mg q8h	75%	100%	q12h	q24h
Zidovudine	200 mg q8h, 300 mg q12h	8%–25%	100%	100%	100 mg q8h

Drugs	Normal Dosage	% of Renal Excretion	GFR >50 mL/min	GFR 10–50 mL/min	GFR <10 mL/min
Alfentanil	Anesthetic induction 8–40 µg/kg	Hepatic	100%	100%	100%
Butorphanol	2 mg intranasally q3–4h	Hepatic	100%	75%	50%
Codeine	30–60 PO mg q4–6h	Hepatic	100%	75%	50%
Fentanyl	Anesthetic induction (individualized)	Hepatic	100%	75%	50%
Meperidine	50–100 mg q3–4h	Hepatic	100%	75%	50%

Comments	HD	CAPD	Continuous Venovenous Hemofiltration
HUS	Dose after dialysis	Dose for GFR < 10 mL/min	Dose for GFR 10–50 mL/min
	None	None	No data: dose for GFR 10–50 mL/min
	50%	50%	50%
Many drug interactions	No data: none	No data: dose for GFR < 10 mL/min	No data: dose for GFR 10–50 mL/min
	No data: none	No data: dose for GFR < 10 mL/min	No data: dose for GFR 10–50 mL/min
	Dose for GFR < 10 mL/min after dialysis	No data	No data: dose for GFR 10–50 mL/min
	Dose for GFR < 10 mL/min after dialysis	No data	No data: dose for GFR 10–50 mL/min
Nephrotoxic	Dose for GFR < 10 mL/min after dialysis	No data	No data: dose for GFR 10–50 mL/min
TTP/HUS; CNS side effects especially in elderly and patients with renal impairment, can cause dehydration	Dose after dialysis	Dose for GFR < 10 mL/min	No data: dose for GFR 10–50 mL/min
Granulocytopenia and thrombocytopenia	Dose after dialysis	Dose for GFR < 10 mL/min	450 mg/day
	Infuse after dialysis	Dose for GFR < 10 mL/min	Dose for GFR 10–50 mL/min
Bioavailability from inhalation and systemic exposure to drug is low	None	None	No data
	No data: dose after dialysis	No data	No data: dose for GFR 10–50 mL/min
Enormous interpatient variation; metabolite renally excreted	Dose for GFR < 10 mL/min	Dose for GFR < 10 mL/min	100 mg q8h

Comments	HD	CAPD	Continuous Venovenous Hemofiltration
Titrate the dose regimen, potent short-acting analgesic widely used in **anesthesia**	N/A	N/A	N/A
	No data	No data	N/A
Prodrug; converted to morphine by CYP2D6	No data	No data	Dose for GFR 10–50 mL/min
CRRT: titrate; inactive metabolites; no significant accumulation in patient with advanced CKD; do not use in opioid-naive patients	N/A	N/A	N/A
Normeperidine, an active metabolite, accumulates in ESRD and may cause seizures; protein binding is reduced in ESRD; 20%–25% excreted unchanged in acidic urine; not for long-term pain	Avoid	Avoid	Avoid

Continued

TABLE 58.3 Antimicrobial Agents in Adult Patients with Chronic Kidney Disease—cont'd

Drugs	Normal Dosage	% of Renal Excretion	GFR >50 mL/min	GFR 10–50 mL/min	GFR <10 mL/min
Methadone	2.5–10 mg q8–12h	Hepatic	100%	100%	50%–75%
Morphine	20–25 mg q4h	Hepatic	100%	75%	50%
Naloxone	0.4–2 mg IV	Hepatic	100%	100%	100%
Pentazocine	50 mg q4h	Hepatic	100%	75%	75%
Propoxyphene	65 mg PO q6–8h	Hepatic	100%	100%	Avoid
Sufentanil	Anesthetic induction	Hepatic	100%	100%	100%
Buprenorphine		27%–30% (3.7% unchanged or active metabolite)	100%	100%	100%
Oxycodone ER		Metabolized extensively by the liver	100%	100%	100%
Oxycodone HCl			100%	100%	100%
Hydrocodone ER	Initial: 15 mg orally every 12 hours	Excreted primarily through renal route	No renal dose adjustment required	No renal dose adjustment required	No renal dose adjustment required
Hydromorphone	2–4 mg PO q 4–6 hours prn	75%, extensively metabolized by liver	100%	CrCl 40–50: 50%; CrCl <30: 25%	CrCl <30: 25%, consider alternative
Acetaminophen	650 mg q4h	Hepatic	q4h	q6h	q8h
Acetylsalicylic acid	650 mg q4h	Hepatic (renal)	q4h	q4–6h	Avoid
Ibuprofen	200–800 mg	45%–79% (1% unchanged)	100%	Avoided	Avoid

Antihypertensive and Cardiovascular Agents	Normal Doses: Starting Dose	Normal Doses: Maximum Dose	% of Renal Excretion	Dosage Adjustment in Renal Failure: GFR >50 mL/min	Dosage Adjustment in Renal Failure: GFR 10–50 mL/min	Dosage Adjustment in Renal Failure: GFR <10 mL/min
ACEIs						
Benazepril	5–10 mg q24h	40 mg q24h	20%	100%	75%	25%–50%
Captopril	6.25–25 mg PO q8h	50 mg TID	>95%	100%	75%	50%
Enalapril	2.5–5 mg q24h	40 mg/day	61%	100%	50–100%	25%

Comments	HD	CAPD	Continuous Venovenous Hemofiltration
Useful in advanced CKD; excreted mainly in feces	None	None	N/A
Increased sensitivity to drug effect in ESRD	None	No data	Dose for GFR 10–50 mL/min
Repeat q2–3 minute prn, call emergency ASAP	N/A	N/A	Dose for GFR 10–50 mL/min
	None	No data	Dose for GFR 10–50 mL/min
Active metabolite norpropoxyphene accumulates in ESRD, lead to cardiotoxicity, used as pain reliever and cough suppressant; MOA unknown	Avoid	Avoid	N/A
CRRT: titrate; anesthesia; metabolize in liver and small intestine	N/A	N/A	N/A
	No, but possible with high doses and concomitant hypoalbuminemia	N/A	N/A
	N/A	N/A	N/A
Higher risk for respiratory depression, accumulation of metabolite hydromorphone-3-glucuronide (H3G) can lead to muscle jerks and delirium symptoms; not as well tolerated in severe CKD	N/A	N/A	N/A
Overdose may be nephrotoxic; drug is major metabolite of phenacetin	None	None	Dose for GFR 10–50 mL/min
Nephrotoxic in high doses; may decrease GFR when RBF is prostaglandin dependent; may add to uremic GI and hematologic symptoms; protein binding reduced in ESRD	Dose after dialysis	None	Dose for GFR 10–50 mL/min
All nonselective NSAIDs or COX-2-specific may cause AKI via attenuation of renal vasodilation. Diuretics, ACEI, ARB, and calcinurin inhibitors ma increase risk of NSAID-induced AKI	None	None	Dose for GFR 10–50 mL/min

Comments	HD and CRRTx	CAPD	Continuous Venovenous Hemofiltration
Hyperkalemia, ARF, angioedema, rash, cough, anemia, and liver toxicity			
	25%–50%	25%–50%	
Rare proteinuria, nephrotic syndrome, dysgeusia, granulocytopenia; increases serum digoxin levels, administer after HD on dialysis days	25%–30%	None	
Enalaprilat, the active moiety, formed in liver, if CrCl can start at 2.5 mg/day but may titrate upward to 40 mg/day as normal.	20%–50%	25%	

Continued

TABLE 58.3 Antimicrobial Agents in Adult Patients with Chronic Kidney Disease—cont'd

	Normal Doses			Dosage Adjustment in Renal Failure		
Antihypertensive and Cardiovascular Agents	**Starting Dose**	**Maximum Dose**	**% of Renal Excretion**	**GFR >50 mL/min**	**GFR 10–50 mL/min**	**GFR <10 mL/min**
Fosinopril	10 mg PO q24h	80 mg/day	20%	100%	100%	100%
Lisinopril	2.5–5 mg/day	40 mg/day	80%	100%	50%–75%	25%–50%
Moexipril	3.75–7.5 mg/day	30 mg/day	7%	100%	50%	50%
Pentopril		125 mg q24h	80%–90%	100%	50%–75%	50%
Perindopril	4 mg	16 mg/day	75%	100%	50%	Not recommended
Quinapril	10 mg q24h	20 mg q24h	30%	100%	75%–100%	75%
Ramipril	2.5 mg q24h	20 mg/day	60%	100%	25%	25%
Trandolapril	1–2 mg q24h	4 mg q24h	33%	100%	50%–100%	50%
Angiotensin II Receptor Antagonists						
Candesartan	8 mg q24h	32 mg q24h	33%	100%	100%	50% (AUC doubled with CrCl < 30)
Eprosartan	600 mg q24h	800 mg/day	37%	100%	100%; max dose 600 mg/day	100%; max dose 600 mg/day
Irbesartan	150 mg q24h	300 mg q24h	20%	100%	100%	100%
Losartan	25–50 mg q24h	100 mg q24h	35%	100%	100%	100%
Olmesartan	20 mg qd	40 mg/day	35%–50%	100%	100%	50%
Telmisartan	20–40 mg q24h	80 mg/day	< 1%	100%	100%	100%
Valsartan	20 mg BID	160 mg BID	13%	100%	100%	Use with caution
ARNI						
Entresto (sacubitril/valsartan)	49/51 mg BID	97/103 mg BID	Sacubitril: 52% to 68%; Valsartan: 13%	100%	100%	100%
Beta-Blockers						
Acebutolol	400 mg q24h or q12h	600 mg q24h or q12h	55%	100%	50%	30%–50%
Atenolol	25 mg q24h	100 mg q24h	90%	100%	75%	50%
Betaxolol	20 mg q24h	80%–90%	100%	100%	50%	50%
Bopindolol	1 mg q24h	4 mg q24h	<10%	100%	100%	100%
Carteolol	0.5 mg q24h	10 mg q24h	<50%	100%	50%	25%

Comments	HD and CRRTx	CAPD	Continuous Venovenous Hemofiltration
Fosinoprilat, the active moiety, formed in liver; drug less likely than other ACEIs to accumulate in renal failure. Initial dose reduction of 5 mg once daily for HF patients	None	None	
Lysine analog of a pharmacologically active enalapril metabolite	50%–100%	None	
	No data	No data	
	No data	No data	
	25%–50%	No data	
Active metabolite is quinaprilat; 96% of quinaprilat is excreted renally	25%	None	
Active metabolite is ramiprilat; data are for ramiprilat	20%	None	
	None	None	
Hyperkalemia, angioedema (less common than ACEIs)			
Candesartan cilexetil is rapidly and completely bioactivated by ester hydrolysis during absorption from the GI tract to candesartan	None	None	None
Eprosartan pharmacokinetics more variable ESRD; decreased protein binding in uremia	None; poorly removed by HD	None	None
Starting dose 75 mg in volume depleted patients	None; nondialyzable	None	None
Monitor closely in renal impairment and in volume depletion	Nondialyzable	No data	None
20 mg max if CrCl < 20 mL/min	No data	No data	None
HD patients are more susceptible to orthostatic hypotension	None; more susceptible to orthostatic hypotension	None	None
	None; not significantly removed	None	None
	No data	No data	
Decrease HDL, mask symptoms of hypoglycemia, bronchospasm, fatigue, insomnia, depression, and sexual dysfunction			
Active metabolites with long half-life	None	None	None
Accumulates in ESRD	25–50 mg	None	None
	None	Dose for GFR 10–50 mL/min	None
	None	None	None
	No data	None	None

Continued

TABLE 58.3 Antimicrobial Agents in Adult Patients with Chronic Kidney Disease—cont'd

Antihypertensive and Cardiovascular Agents	Normal Doses			Dosage Adjustment in Renal Failure		
	Starting Dose	Maximum Dose	% of Renal Excretion	GFR >50 mL/min	GFR 10–50 mL/min	GFR <10 mL/min
Carvedilol	3.125 mg PO q8h	25 mg q8h	2%	100%	100%	100%
Celiprolol		200 mg q24h	10%	100%	100%	75%
Dilevalol	200 mg q12h	400 mg q12h	<5%	100%	100%	100%
Esmolol (IV only)	50 µg/kg/min	300 µg/kg/min	10%	100%	100%	100%
Labetalol	50 mg PO q12h	400 mg q12h	5%	100%	100%	100%
Metoprolol		50 mg q12h	100 mg q12h	<5%	100%	100%
Nadolol	80 mg q24h	160 mg q12h	90%	100%	50%	25%
Penbutolol	10 mg q24h	40 mg q24h	<10	100%	100%	100%
Pindolol	10 mg q12h	40 mg q12h	40%	100%	100%	100%
Propranolol	40 mg–160 mg q8h	320 mg/day	<5%	100%	100%	100%
Sotalol	80 q12h	160 mg q12h	70%	100%	50%	25%–50%
Timolol	10 mg q12h	20 mg q12h	15%	100%	100%	100%
Calcium Channel Blockers						
Amlodipine	2.5 PO q24h	10 mg q24h	10%	100%	100%	100%
Bepridil	No data	<1%	No data	No data	No data	
Diltiazem	30 mg q8h	120 mg q8h	35%	100%	100%	100%
Felodipine	5 mg PO q24h	10 mg q24h	70%	100%	100%	100%
Isradipine	5 mg PO q12h	10 mg q12h	60%–65%	100%	100%	100%
Nicardipine	20 mg PO q8h	40 mg PO q8h	60%	100%	100%	100%
Nifedipine XL	30 q24h	90 mg q12h	60%–80%	100%	100%	100%
Nimodipine	60 mg q4h × 21 consecutive days (subarachnoid hemorrhage)		10%	100%	100%	100%
Nisoldipine	20 mg q24h	40 mg q24h	60%–80%	100%	100%	100%
Verapamil	40 mg q8h	360 mg/day	70%	100%	100%	100%

Comments	HD and CRRTx	CAPD	Continuous Venovenous Hemofiltration
Kinetics are dose dependent; plasma concentrations of carvedilol have been reported to be increased in patients with renal impairment	None	None	None
	No data	None	None
	None	None	None
Active metabolite retained in renal failure	None	None	None
For IV use: 20 mg slow IV injection over a 2-minute period; additional injections of 40 mg or 80 mg can be given at 10-minute intervals until a total of 300 mg or continuous infusion of 2 mg/min	None	None	None
	None	None	None
Start with prolonged interval and titrate	40 mg	None	None
	None	None	None
	None	None	None
Bioavailability may increase in ESRD; metabolites may cause increased bilirubin by assay interference in ESRD; hypoglycemia reported in ESRD	None	None	None
Extreme caution should be exercised in the use of sotalol in patients with renal failure undergoing HD; to minimize the risk of induced arrhythmia; patients initiated or reinitiated on sotalol should be placed for a minimum of 3 days (on their maintenance dose) in a facility that can provide cardiac resuscitation and continuous ECG monitoring	80 mg	None	None
	None	None	None
Dihydropyridine: headache, ankle edema, gingival hyperplasia, and flushing, nondihydropyridine: bradycardia, constipation, gingival hyperplasia, and AV block			None
May increase digoxin and cyclosporine levels	None	None	None
Weak vasodilator and antihypertensive. **D/C in the United States**	None	No data	None
Acute renal dysfunction; may exacerbate hyperkalemia; may increase digoxin and cyclosporine levels	None	None	None
May increase digoxin levels	None	None	None
May increase digoxin levels	None	None	None
Uremia inhibits hepatic metabolism; may increase digoxin levels	None	None	None
Avoid short-acting nifedipine formulation	None	None	None
May lower BP	None	None	None
May increase digoxin levels	None	None	None
Acute renal dysfunction; active metabolites accumulate, particularly with sustained-release forms	None	None	None

Continued

TABLE 58.3 Antimicrobial Agents in Adult Patients with Chronic Kidney Disease—cont'd

Antihypertensive and Cardiovascular Agents	Normal Doses			Dosage Adjustment in Renal Failure		
	Starting Dose	Maximum Dose	% of Renal Excretion	GFR >50 mL/min	GFR 10–50 mL/min	GFR <10 mL/min
Diuretics						
Acetazolamide	250 mg IV QD	375 mg IV QD	90%	100%	50%	Avoid
Amiloride	5 mg PO q24h	10 mg PO q12h	50%	100%	50%	Avoid
Bumetanide	1–2 mg PO q24h	2–4 mg PO q24h	81%	100%	100%	100%; use with caution
Chlorthalidone	25 mg q24h	200 mg/day	50% to 74%	100%	100%	Ineffective with low GFR; avoid use
Ethacrynic acid	50 mg PO q24h	400 mg/day	66%	100%	100%	100%; use with caution
Furosemide	40 mg PO q24h	600 mg/day	60 to 90%	100%	100%;	100%
Indapamide	1.25 mg q24h	5 mg QD	60 to 70%	100%	1.25 to 2.5 mg QD	1.25 to 2.5 mg QD (limited data)
Metolazone	2.5 mg PO q24h	20 mg/day	56%	100%	100%	100%
Eplerenone	25 mg/day	300 mg/day	67%	100%	GFR 31–49: 25 mg QOD, max 25 mg QD	GFR <30: not recommended
Spironolactone	12.5 mg PO q24h	400 mg PO q24h	47% to 57%	100%	50%	Avoid
HCTZ	25 mg q12h	200 mg/day	61%	100%	100%	Avoid
Torsemide	5 mg PO QD	200 mg/day	25%	Adjust dose based on degree of renal impairment (no specific guidance given)	Adjust dose based on degree of renal impairment (no specific guidance given)	Adjust dose based on degree of renal impairment (no specific guidance given)
Triamterene	25 mg q12h	300 mg/day	21%	Adjust dose based on degree of renal impairment (no specific guidance given)	Adjust dose based on degree of renal impairment (no specific guidance given); avoid in severe disease	Adjust dose based on degree of renal impairment (no specific guidance given); avoid in severe disease

Comments	HD and CRRTx	CAPD	Continuous Venovenous Hemofiltration
Hypokalemia or hyperkalemia (potassium-sparing agents), hyperuricemia, hyperglycemia, hypomagnesemia, increase serum cholesterol			None
May potentiate acidosis; ineffective as diuretic in ESRD may cause neurologic side effects in dialysis patients	Dialyzable; avoid use unless dose is reduced and serum concentrations monitored	Supplemental dose not necessary	None
Hyperkalemia with GFR < 30 mL/min, especially in diabetics; hyperchloremic metabolic acidosis; contraindicated in anuria, acute or chronic renal insufficiency, or diabetic nephropathy	No data	No data	None
Ototoxicity increased in ESRD in combination with aminoglycosides; high doses effective in ESRD; muscle pain, gynecomastia; contraindicated in anuria	No data	No data	None
Contraindicated in anuria	No data	No data	None
Ototoxicity increased in ESRD in combination with aminoglycosides; contraindicated in anuria	No data	No data	None
Ototoxicity increased in ESRD, especially in combination with aminoglycosides; high doses effective in ESRD; avoid in oliguric states	Nondialyzable; no supplemental dose needed	Nondialyzable; no supplemental dose needed	None
	1.25 to 2.5 mg QD (limited data); nondialyzable	No data	None
High doses effective in ESRD	No data	No data	None
Hyperkalemia, gynecomastia, impotence	Nondialyzable	No data	None
Active metabolites with long half-life; hyperkalemia common when GFR < 30, especially in diabetics; gynecomastia, hyperchloremic acidosis; increases serum by immunoassay interference	Avoid	Avoid	Avoid
Usually ineffective with GFR < 30 mL/min; effective at low GFR in combination with loop diuretic; hyperuricemia	No data	No data	
High doses effective in ESRD; ototoxicity	No data	No data	
Hyperkalemia common when GFR < 30, especially in diabetics; active metabolite with long half-life in ESRD; folic acid antagonist; urolithiasis; crystalluria in acid urine; may cause ARF; avoid in severe impairment, progressive kidney disease, or anuria	Avoid	Avoid	

Continued

TABLE 58.3 Antimicrobial Agents in Adult Patients with Chronic Kidney Disease—cont'd

	Normal Doses			Dosage Adjustment in Renal Failure		
Antihypertensive and Cardiovascular Agents	**Starting Dose**	**Maximum Dose**	**% of Renal Excretion**	**GFR >50 mL/min**	**GFR 10–50 mL/min**	**GFR <10 mL/min**
Amiodarone	Initial: 300 mg IV over 1 hour, then 10 to 50 mg/h over 24 hours; maintenance: 100–200 PO QD	200 mg	<1%	100%	100%	100%
Clonidine	0.1 mg PO q12h	2.4 mg/day	40%–60%	Adjust dose based on degree of renal impairment (no specific guidance given)	Adjust dose based on degree of renal impairment (no specific guidance given)	Adjust dose based on degree of renal impairment (no specific guidance given)
Digoxin	0.125 mg PO q24h	0.25 mg PO q24h	50%–70%	100%	0.0625 mg q24–36h (25%–75%)	0.0625 mg q48h (10%–25%)
Hydralazine	10 mg PO q6–8h	100 mg PO q6–8h	3% to 14%	100% q6–8h	100% q6–8h	100% q8–16h
Midodrine	2.5 mg PO TID	10 mg PO TID	40% to 75%	5–10 mg TID	2.5 mg TID (gradually increase as tolerated)	2.5 mg TID (gradually increase as tolerated)
Minoxidil	5 mg PO QD	100 mg/day	90%	Adjust dose based on degree of renal impairment (no specific guidance given)	Adjust dose based on degree of renal impairment (no specific guidance given)	Adjust dose based on degree of renal impairment (no specific guidance given)
Nitroprusside	0.3–0.5 μg/kg/min	10 μg/kg/min	Extensive as metabolite (thiocyanate)	100%	100%; GFR <30 limit infusion rate to <3 μg/kg/min	Limit infusion rate to <3 μg/kg/min; anuric = limit to 1 μg/kg/min
Amrinone (NOT used in the United States)	5 μg/kg/min	10 μg/kg/min	10%–40%	100%	100%	100%
Dobutamine	0.5–2.5 μg/kg/min	40 μg/kg/min	66%	100%	100%	100%
Milrinone	0.125 μg/kg/min	0.75 μg/kg/min	40% to 75%	100%	0.0625 to 0.125 μg/kg/min	Consider alternative therapy
Ivabradine	2.5–5 mg BID	7.5 mg BID	4%	100%	100%	CrCl <15 has not been studied
Dofetilide	500 μg BID	500 μg BID	80%	100%	CrCl 40–60: 250 μg BID; CrCl 20–39: 125 μg BID	CrCl < 20 use is contraindicated
Nitroglycerin	10 μg/min IV	400 μg/min IV	22%	100%	100%	100%
Isosorbide mononitrate	IR: 20 mg BID; ER: 30–60 mg QD	240 mg QD	93% to 96%	100%	100%	100%

Comments	HD and CRRTx	CAPD	Continuous Venovenous Hemofiltration
Thrombocytopenia; nausea, vomiting in ESRD	No data	No data	
Sexual dysfunction, dizziness, portal hypotension; half-life increased up to 41 hours in severe renal impairment	Not dialyzable (0%–5%) so no adjustment needed	No data	
Decrease loading dose by 50% in ESRD; radioimmunoassay may overestimate serum levels in uremia; clearance decreased by amiodarone, spironolactone, quinidine, verapamil; hypokalemia, hypomagnesemia enhance toxicity; V_d and total body clearance decreased in ESRD; serum level 12 hours after dose is the best guide in ESRD; digoxin immune antibodies can treat severe toxicity in ESRD	Nondialyzable; dose for GFR < 10	Dose for GFR < 10	
Lupus-like reaction	Dose after HD	Dose for GFR < 10	
Increased BP	5 mg q8h; dialyzable	No data	
Pericardial effusion, fluid retention, hypertrichosis, and tachycardia	No data	No data	
Cyanide toxicity	No data	Dialyzable	
Thrombocytopenia; N/V in ESRD	No data	No data	
Tachyarrhythmia	No data	No data	
Dysuria	Dialyzable	No data	
Should be given with beta-blocker, in HR > 70	No data	No data	
Must continuously monitor ECG for Torsades after each dose, must know CrCl and QTc before first dose	No data	No data	
HA, careful of tolerance	No data	No data	
	Dose after HD, no supplemental dose needed	No data	

Continued

TABLE 58.3 Antimicrobial Agents in Adult Patients with Chronic Kidney Disease—cont'd

Antihypertensive and Cardiovascular Agents	Normal Doses: Starting Dose	Normal Doses: Maximum Dose	% of Renal Excretion	Dosage Adjustment in Renal Failure: GFR >50 mL/min	Dosage Adjustment in Renal Failure: GFR 10–50 mL/min	Dosage Adjustment in Renal Failure: GFR <10 mL/min
Isosorbide dinitrate	5–20 mg BID-TID	80 mg BID-TID	80% to 90%	100%	100%	100%
Hypoglycemic Agents						
Acarbose	25 mg q8h	100 mg q8h	35%	100%	50%	Avoid
Acetohexamide	250 mg q24h	1500 mg q24h	None	Avoid	Avoid	Avoid
Canagliflozin	100 mg q24h	300 mg qd	None	45–<60 mL/min: max 100 mg qd	30–<45 mL/min: avoid	< 30 mL/min: contraindication
Chlorpropamide	100 mg q24h	500 mg q24h	47%	50%	Avoid	Avoid
Dapagliflozin	5 mg QD	10 mg QD	None	≥ 60 mL/min: 100%	< 60 mL/min: avoid	< 30 mL/min: contraindication
Dulaglutide	0.75 mg SQ weekly	1.5 mg SQ weekly	No data	100%	100%	100%
Emphagliflozin	10 mg QD	25 mg QD	None	≥ 45 mL/min: 100%	< 45 mL/min: avoid	< 30 mL/min: contraindication
Exenatide	IM: 5 µg SQ BID. ER: 2 mg SQ weekly	IM: 10 µg SQ BID	No data	100%	50%	Avoid
Glibornuride	12.5 mg q24h	100 mg q14h	No data	No data	No data	No data
Gliclazide	80 mg q24h	320 mg q24h	< 20%	50%–100%	Avoid	Avoid
Glipizide	5 mg q24h	20 mg q12h	5%	100%	50%	50%
Glyburide	2.5 mg q24h	10 mg q12h	50%	100%	50%	Avoid
Liraglutide	0.6 mg SQ QD	1.8 mg SQ QD	6%	100%	100%	Avoid
Lixisenatide	10 µg SQ QD	20 µg QD	No data	100%	15–30 mL/min: close monitoring	<15 mL/min: avoid
Metformin	500 mg q12h	2550 mg/day (q12h or q8h)	95%	100%	Avoid	Avoid
Pioglitazone	15–30 mg q24h	45 mg q24h	15%–30%	100%	100%	100%
Pramlintide	15 µg	60 µg daily	No data	100%	No data	No data
Repaglinide	0.5–1 mg	4 mg q8h				
Rosiglitazone	4 mg q24h	8 mg q24h	64%	100%	100%	100%
Semaglutide	PO: 3 mg–7 mg QD. SQ: 0.25–0.5 mg weekly	P0: 14 mg QD. SQ: 1 mg weekly	3%	100%	100%	100%
Sitagliptin	25 mg	100 mg	79%	100%	50%	25%
Tolazamide	100 mg q24h	250 mg q24h	7%	100%	100%	100%

Comments	HD and CRRTx	CAPD	Continuous Venovenous Hemofiltration
	No supplemental dose needed	No supplemental dose needed	
Avoid all oral hypoglycemic agents on CRRT			
Abdominal pain, N/V, and flatulence	Avoid	Avoid	Avoid
Diuretic effect; may falsely elevate serum creatinine; active metabolite has $t_{1/2}$ of 5–8 hours in healthy subjects and is eliminated by the kidney; prolonged hypoglycemia in azotemic patients	Avoid	Avoid	Avoid
BBW: Lower limb amputation. Common SE: UIT, hypovolemia, electrolyte abnormality (hyperkalemia), risk of euglycemix ketoacidosis	Contraindication	Contraindication	Contraindication
Impairs water excretion; prolonged hypoglycemia in azotemic patients	Avoid	Avoid	Avoid
No BBW. SEs (see canagfliflozin)	Contraindication	Contraindication	Avoid
BBW: thyroid tumors. Common SE: N/V/D, weigh loss.	No data	No data	Avoid
No BBW. SEs (see canagliflozin) only cana- and empa- have ASCVD benefits, HF, DKD	Contraindication	Contraindication	Avoid
BBW: thyroid C cells tumors (Bydureon: ER). Common SE: N/V/D, hypoglycemia. Last 30 days after opening	Avoid	Avoid	Avoid
	Avoid	Avoid	Avoid
	Avoid	Avoid	Avoid
	Avoid	Avoid	Avoid
	Avoid	Avoid	Avoid
BBW: increased risk of thyroid cancer. Also use in weight loss. SE: N/V/D, hypoglycemia. Lira-, sema-: ASCVD benefits	Avoid	Avoid	Avoid
SE: GI symptoms	Avoid	Avoid	Avoid
Lactic acidosis	Avoid	Avoid	Avoid
Contraindicated in NYHA HF III–IV. Caution in impaired hepatic function or injury, can lead to liver failure. Associated with weight gain. Multiple drug interactions.	Avoid	Avoid	Avoid
	Avoid	Avoid	Avoid
	Avoid	Avoid	Avoid
Increases LDL. Contraindicated in HF, NYHA III–IV. Associated with weight gain. Caution in patients with hepatic impairment or injury, rosiglitazone can induce liver failure.	None	None	Avoid
BBW: thyroid C cells tumor. Common SE: GI upset	No data	No data	Avoid
Diuretic effects	Avoid	Avoid	Avoid

Continued

TABLE 58.3 Antimicrobial Agents in Adult Patients with Chronic Kidney Disease—cont'd

Antihypertensive and Cardiovascular Agents	Normal Doses			Dosage Adjustment in Renal Failure		
	Starting Dose	Maximum Dose	% of Renal Excretion	GFR >50 mL/min	GFR 10–50 mL/min	GFR <10 mL/min
Tolbutamide	1 g q24h	2 g q24h	None	100%	100%	100%
Insulin Agents						
Insulin regular	4 to 6 units or 0.1 units/kg or 10% of basal dose	Titrate to desired BG range	Largely via urine	100%	75% or normal dose	50% or normal dose
Lispro insulin	4 to 5 units or 10% of basal dose	Titrate to desired BG range	Largely via urine	100%	More frequent dose adjustments and monitoring may be needed	More frequent dose adjustments and monitoring may be needed
Insulin glargine	10 units or 0.1 to 0.2 units/kg/day	Titrate to desired BG range	Largely via urine	100%	More frequent dose adjustments and monitoring may be needed	More frequent dose adjustments and monitoring may be needed

Hyperlipidemic Agents	Normal Doses			Dosage Adjustment in Renal Failure		
	Starting Dose	Maximum Dose	% of Renal Excretion	GFR >50 mL/min	GFR 10–50 mL/min	GFR <10 mL/min
Alirocumab	75 mg SQ q 2 weeks	150 mg SQ q 2 weeks	0%	100%	100%	100%
Atorvastatin	10 mg/day	80 mg/day	<2%	100%	100%	100%
Bezafibrate	200 mg TID OR 400 mg once (SR)		50%	100%	50%	Avoid
Cholestyramine	4 g q12h	24 g/day	None	100%	100%	100%
Clofibrate	500 mg q12h	1000 mg q12h	40%–70%	q6–12h	q12–18h	q24–48h
Colestipol	5 g q12h	30 g/day	None	100%	100%	100%
Evolocumab	140 mg SQ q 2 weeks OR 420 mg monthly		None	100%	100%	100%
Ezetimibe	10 mg/day		11%	100%	100%	100%
Fenofibrate	48 g/day	145 g/day	60%–93%	100%	100%	Avoid
Fluvastatin	20 g/day	80 g/day	5%	100%	100%	100%
Gemfibrozil	600 q12h	600 q12h	70%	100%	75%	50%
Lovastatin	20 mg/day	80 mg/day	10%	100%	100%	100%
Nicotinic acid	1 g q8h	2 g q8h	60%–76%	100%	100%	100%
Pitavastatin	1 mg QD	4 mg QD	15%	100%	50%	50%
Pravastatin	10–40 mg/day	80 mg/day	20%	100%	100%	100%
Probucol		500 mg q12h	<2%	100%	100%	100%
Rosuvastatin	5 mg/day	40 mg/day	<5%	100%	100%	Initial: 5 mg QD. max 10 mg/day
Simvastatin	5–20 mg/day	80 mg/day	13%	100%	100%	100%

Comments	HD and CRRTx	CAPD	Continuous Venovenous Hemofiltration
May impair water excretion	Avoid	Avoid	Avoid
Dosage guided by blood glucose levels	Avoid	Avoid	Avoid
Caution for hypoglycemia. Caution for hypokalemia. Renal excretion of insulin decreases with azotemia. Risk of hypoglycemia increases with hepatic and renal impairment.	100%	100%	100%
Caution for hypoglycemia. Caution for hypokalemia. Risk of hypoglycemia increases with hepatic and renal impairment.		100%	100%
Caution for hypoglycemia, caution for hypokalemia. Risk of hypoglycemia increases with hepatic and renal impairment.	N/A	100%	100%

Comments	HD	CAPD	Continuous Venovenous Hemofiltration
	100%	100%	100%
Liver dysfunction, myalgia, and rhabdomyolysis with CSA/FK	50%	50%	50%
No data	100%	Avoid	Avoid
	100%	100%	100%
	100%	100%	100%
	100%	100%	100%
	100%	100%	100%
	50%	50%	50%
CI in GFR <30 and dialysis	100%	100%	100%
	100%	100%	100%
Take 30 minutes before meal	100%	100%	100%
GFR <30, use with caution and carefully consider doses >20 mg/day	100%	100%	100%
Not first or second line in patients with dyslipidemia	100%	100%	100%
	50%	50%	50%
	100%	100%	100%
Removed from market in United States in 1995.	50%	50%	50%
GFR <30: max 10 mg/day	100%	100%	100%
	100%	100%	100%

Continued

TABLE 58.3 Antimicrobial Agents in Adult Patients with Chronic Kidney Disease—cont'd

Anticonvulsants (290)	Normal Doses		% of Renal Excretion	Dosage Adjustment in Renal Failure		
	Starting Dose	Maximum Dose		GFR >50 mL/min	GFR 10–50 mL/min	GFR <10 mL/min
Carbamazepine	200 mg BID	1200 mg/day	72% (3% unchanged)	100%	100%	Moderate to severe renal impairment, carbamazepine should generally not be used
Clonazepam	0.5 mg q8h	20 mg/day	Less than 2%	100%	100%	100%
Ethosuximide	500 mg/day	1.5 g/day	10%–20%	100%	100%	
Felbamate	400 mg/q8h	1200 mg/q8h	90%	100%	50%	25%
Gabapentin	300 mg q8h	2400 mg/day	76%–81%	100%	50%	25%
Lamotrigine	25–50 mg/day	500 mg/day	94%	100%	100%	100%,
Levetiracetam	500 mg q12h	1500 mg q12h	66%	100%	50%	50%
Oxcarbazepine	300 mg q12h	2400 mg/day	More than 95%, less than 1% unchanged	100%	100%	CrCl <30 mL/min
Phenobarbital	50–100 mg PO BID-TID	Adjust to maintain therapeutic serum concentration	21%	100%	100%	100%
Phenytoin	100 mg q8	600 mg/day	Excreted in urine after reabsorption from intestinal tract	100%	100%	100%
Primidone	100 mg QD-TID	2000 mg/day	1%	100%	100%	100%
Sodium valproate	7.5–15 mg/kg/day; adjust for side effect and TDM		1%	100%	100%	100%
Tiagabine	4 mg q24h, increase 4 mg/day, titrate weekly		2%	100%	100%	100%
Topiramate	50 mg/day	200 mg q12h	70%	100%	50%	Avoid
Trimethadione	300 mg q6h–q8h	600 mg q6h–q8h	None	q8h	q8h–q12h	q12h–q24h
Vigabatrin	1 g q12h	2 g q12h	70%	100%	50%	25%
Zonisamide	100 mg q24h	100–300 mg q12h–q24h	30%	100%	75%	50%

Comments	HD	CAPD	
Plasma concentration: 4–12 μg/mL, myelosuppression, CYP3A4 inducer, fluid retention	N/A	N/A	No data
No renal dose adjustments	None	No data	No data
Plasma concentration: 40–100 mg/L, headache 100%, no renal dose adjustments but renal function abnormalities have been reported; use caution in patients with renal disease and monitoring recommended	No data	No data	No data
Anorexia, vomiting, insomnia, nausea	Dose after dialysis	No data	No data
Fewer CNS side effects than to other agents CrCl 15–29 mL/min: 200–700 mg/day QD CrCl 15 mL/min: 100–300 mg/day QD CrCl < 15 mL/min: reduce daily dose in proportion to CrCl	After 4-hour session, give supplemental dose of 125 mg for maintenance daily dose of 100 mg	No data	No data
Autoinduction, major drug–drug interaction with valproate reduced maintenance dose may be effective	No data	No data	No data
	500–1000 mg Q24 and 250–500 mg after dialysis	No data	No data
Less effect on P450 compared with carbamazepine Extended release initially 300 mg/day, may increase at 300–450 mg/day increments	Use immediate release instead of extended release	No data	No data
Plasma concentration: 10–40 mg/L, no renal dose adjustments	No data	No data	No data
Plasma concentration: 10–20 μg/mL, nystagmus, check free phenytoin level	No data	No data	No data
Plasma concentration: 5–20	One-third dose following HD	No data	No data
Plasma concentration: 50–150; weight gain; hepatitis; check free valproate level	None	None	
Total daily dose may be increased by 4–8 mg at weekly intervals until clinical response is achieved or up to 32 mg/day; total daily dose should be given in divided doses two to four times daily	None	None	
	No data	No data	No data
Active metabolites with long half-life in ESRD; nephrotic syndrome	No data	No data	No data
Encephalopathy with drug accumulation	No data	No data	No data
	Dose for GFR < 10 mL/min	Dose for GFR < 10 mL/min	No data

Continued

TABLE 58.3 Antimicrobial Agents in Adult Patients with Chronic Kidney Disease—cont'd

Arthritis and Gout Agents	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure		
			GFR >50 mL/min	GFR 10–50 mL/min	GFR <10 mL/min
Allopurinol	300 mg q24h	30	75%	50%	25%
Auranofin	6 mg q24h	50	50%	Avoid	Avoid
Colchicine	Acute: 2 mg; then 0.5 mg q6h Chronic: 0.5–1.0 mg q24h	5–17	100%	50%–100%	25%
Gold sodium	25–50 mg	60–90	50%	Avoid	Avoid
Penicillamine	250–1000 mg q24h	40	100%	Avoid	Avoid
Probenecid	500 mg q12h	<2	100%	Avoid	Avoid
Pegloticase	8 mg IV q2wk	No data	100%	100%	100%
Febuxostat	40–80 mg PO daily	3%	100%	100%	50%
Nonsteroidal Anti-Inflammatory Drugs	May decrease renal function; decrease platelet aggregation; nephrotic syndrome; interstitial nephritis; hyperkalemia, sodium retention KDIGO: NSAIDs not recommended in GFR 30–60 mL/min if the patient is at risk for AKI; avoid NSAIDs in GFR <30 Topical NSAIDs appear to be safe as systemic absorption				
Diclofenac	25–100 mg q24h	65	100%	25%–50%	Avoid
Diflunisal	500–1000 mg q12h	80–90	100%	50%	50%
Etodolac	300–500 mg q12h	70	100%	100%	100%
Fenoprofen	300–600 mg q6h	90	100%	100%	100%
Flurbiprofen	200–300 mg q23h	20	100%	Contraindicated in GFR <30	Contraindicated in GFR <30
Ibuprofen	200–800 mg q6–8h	45–80	100%	100%	Avoid
Indomethacin	25–50 mg q8h	60	100%	Not recommended	Avoid
Ketoprofen	25–75 mg q8h	80	100%	MAX 150 mg/day if GFR >25; MAX 100 mg/day if GFR <25	Avoid
Ketorolac	30–60 mg load; then 15–30 mg q6h	92	100%	MAX 60 mg/day	Avoid
Meclofenamic acid	50–100 q6h–q8h	2–4	100%	100%	Avoid
Mefenamic acid	250 mg q6h	<6	100%	100%	Avoid
Nabumetone	1.0–2.0 g q24h	<1	100%	50%–100%	Avoid
Naproxen	500 mg q12h	<1	100%	100%	Avoid
Oxaprozin	1200 mg q24h	<1	100%	100%	Avoid
Phenylbutazone	100 mg q6h–q8h	1	100%	100%	Avoid
Piroxicam	20 mg q24h	10	100%	100%	Avoid
Sulindac	200 mg q12h	7	100%	100%	Avoid
Tolmetin	400 mg q8h	15	100%	100%	100%

Comments	HD	CAPD	Continuous Venovenous Hemofiltration CRRTx
Interstitial nephritis; rare xanthine stones			No data
Renal excretion of active metabolite with $t_{1/2}$ of 25 hours in normal renal function; $t_{1/2}$ 1 week in patients with ESRD; exfoliative dermatitis	No data	Dose for GFR 10–50 mL/min	No data
Proteinuria and nephritic syndrome	None	None	No data
Avoid prolonged use if GFR < 50 mL/min	No data	Dose for GFR 10–50 mL/min	No data
			No data
Thiomalate proteinuria; nephritic syndrome; membranous nephritis	None	Avoid	No data
Nephrotic syndrome	No data	Dose for GFR 10–50 mL/min	No data
Ineffective at decreased GFR	No data	Avoid	No data
			No data
No data	No data	No data	No data
No data	Avoid	Avoid	Avoid
50%	Avoid	Avoid	Avoid
100%	Avoid	Avoid	Avoid
100%	Avoid	Avoid	Avoid
No data	Avoid	Avoid	Avoid
No data	Avoid	Avoid	Avoid
No data	Avoid	Avoid	Avoid
No data	Avoid	Avoid	Avoid
Acute hearing loss in ESRD	Avoid	Avoid	Avoid
None			
None	Avoid	Avoid	Avoid
None	Avoid	Avoid	Avoid
None	Avoid	Avoid	Avoid
None	Avoid	Avoid	Avoid
None	Avoid	Avoid	Avoid
None	Avoid	Avoid	Avoid
None	Avoid	Avoid	Avoid
Active sulfide metabolite in ESRD	Avoid	Avoid	Avoid
None			
None	None	Dose for GFR 10–50 mL/min	No data

Continued

TABLE 58.3 Antimicrobial Agents in Adult Patients with Chronic Kidney Disease—cont'd

Drugs	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure: GFR >50 mL/min	GFR 10–50 mL/min	GFR <10 mL/min
Bisphosphonate—alendronate	10 mg QD or 70 mg once a week; 40 mg QD for 6 months—Paget disease	30%–50% in 24 hours	eGFR 35–60 mL/min no dose adjustment needed	50%	50%
Zoledronic acid	5 mg IV infused over 15 minutes once a year	39% ± 16% unchanged	No dose adjustments	50%	50%
Teriparatide	20 μg SQ once daily	Unknown	No dose adjustments	Mild to moderate—no changes	A significant increase in $t_{1/2}$ and AUC (75%) but not plasma levels with severe renal impairment
Risedronate	5 mg PO QD, 35 mg PO once weekly, or 75 mg PO two consecutive days for a total of two tablets per month	50%	No dose adjustments	Less than 30 not recommended	NR
Ibandronate	150 mg orally once monthly OR 3 mg IV infused over 15 to 30 seconds every 3 months	50%–60%	No dose adjustments	<30 mL/min not recommended	NR
Abaloparatide	80 mg SQ QD, given with supplemental Ca and vitamin D	N/A	No renal dose adjustments		

Cholinesterase Inhibitors	Normal Dosage	% of Renal Excretion	GFR >50	GFR 10–50 mL/min	GFR <10 mL/min
Donepezil	5 mg QD	79%	No renal adjustment required		
Galantamine	IR: 4 mg BID ER: 8 mg QD	20%–25%	10–60 mL/min: MAX 16 mg/day		Not recommended
Rivastigmine	1.5 mg BID	97%	No renal adjustment required		

Stimulants	Starting Dose	% of Renal Excretion	GFR >30 mL/min	GFR 15–30 mL/min	GFR <15 mL/min
Methylphenidate IR	5 mg BID	78%–98%	No data	No data	No data
Dextroamphetamine/amphetamine IR	5 mg QAM or BID	30%–40% unchanged	There are no dosage adjustments provided in the manufacturer's labeling; use with caution; the potential exists for elimination of amphetamine to be inhibited resulting in prolonged exposure.		

Comments	HD	CAPD	Continuous Venovenous Hemofiltration
SE— ulcerative esophagitis, GI upset, intolerance, jaw osteonecrosis, a fib counsel on: take on empty stomach with 8 oz water in upright position and remain upright for at least 30 minutes; stop treatment after 5 years in most patients	None	None	None
GI upset/intolerance, jaw osteonecrosis, should be given over no less than 15 minutes to avoid renal failure	None	None	None
Avoid in patients with severe renal impairment, max 2 years treatment due to risk of osteosarcoma; orthostatic hypotension; may cause hypercalcemia	None	None	None
Delayed release taken AFTER food; contraindicated in esophageal abnormalities (stricture, achalasia) that delay esophageal emptying, CI hypocalcemia	None	None	None
Need to wait 60 minutes before eating or lying down; CI esophageal abnormalities, hypocalcemia	None	None	None
Potential for hypercalcemia avoid use in preexisting hypercalcemia; may cause orthostatic hypotension;	None	None	None

Comments	HD	CAPD	Continuous Venovenous Hemofiltration	
Approved for all stages		100%	100%	100%
Associated with QT prolongation, bradycardia, weight loss, rare cases of neuroleptic malignant syndrome				
Approved for mild to moderate. CNS depression, skin reaction, bradycardia, weight loss.		100%	100%	100%
Approved for mild to moderate CNS depression, skin reaction, bradycardia, weight loss		1005	100%	100%

Comments	HD	CAPD	Continuous Venovenous Hemofiltration
Take 30 minutes before breakfast or lunch	No data	No data	No data
Contraindications: pheochromocytoma, adrenal medulla tumor			
Misuse can cause sudden death and serious CV events	Dextroamphetamine is not dialyzable	No data	No data

Continued

TABLE 58.3 Antimicrobial Agents in Adult Patients with Chronic Kidney Disease—cont'd

Stimulants	Starting Dose	% of Renal Excretion	GFR >30 mL/min	GFR 15–30 mL/min	GFR <15 mL/min
Lisdexamfetamine	30 mg QAM	96%	100%	Max dose: 50 mg/day	Max dose: 30 mg/day
Nonstimulants					
Atomoxetine	40 mg/day	80%	100%	100%	100%
Guanfacine ER	1 mg/day	50%	There are no specific dosage adjustments provided in the manufacturer's labeling; however, the lower end of the dosing range is recommended in patients with renal impairment.		

Mood Stabilizers	Starting Dose	% of Renal Excretion	GFR >50 mL/min	GFR 10–50 mL/min	GFR <10 mL/min
Lithium	150–900 mg/day divided TID	89%–98%	Initiate at low dose and titrate slowly	Avoid use	

			Dosage Adjustment in Renal Failure		
Corticosteroids	Normal Dosage	% of Renal Excretion	GFR >50 mL/min	GFR 10–50 mL/min	GFR <10 mL/min
Betamethasone	0.5–9.0 mg q24h	5	100%	100%	100%
Budesonide	64 µg–9 mg q24h	60	100%	100%	100%
Cortisone	25–300 mg q24h	1	100%	100%	100%
Dexamethasone	0.75–9.0 mg q24h	10	100%	100%	100%
Fludrocortisone	0.05–0.2 mg q24h	No data	100%	100%	100%
Hydrocortisone	20–500 mg q24h	1	100%	100%	100%
Methylprednisolone	4–60 mg q24h	<10	100%	100%	100%
Prednisolone	5–60 mg q24h	No data	100%	100%	100%
Prednisone	5–60 mg q24h	No data	100%	100%	100%
Triamcinolone	60 mg q24h	40–75	100%	100%	100%

Antidepressants	Starting Dose	% of Renal Excretion	GFR >60 mL/min	GFR 30–60 mL/min	GFR <30 mL/min
SSRIs					
Fluoxetine	20 mg/day	2.5%–5% unchanged	100%	100%	100%

Comments	HD	CAPD	Continuous Venovenous Hemofiltration
Low abuse potential (if injected or snorted, there is no fast rush effect)	Max dose: 30 mg/day	No data	No data
Second line for ADHD when stimulant medications have failed			
Contraindication: MAOi use within the past 14 days	No data	No data	No data
Do not open the capsule			
Dose-dependent CV effects (bradycardia, hypotension, orthostasis, syncope)	No data	No data	No data
Causes sedation and drowsiness			
Do not d/c abruptly because of rebound hypertension			

Comments	HD	CAPD	Continuous Venovenous Hemofiltration
Avoid in pregnancy (Category D)	No data	No data	No data
Therapeutic range: 0.6–1.2 mEq/L (trough level)			

Comments	HD	CAPD	Continuous Venovenous Hemofiltration
Extensively metabolized by liver, kidney excretes inactive metabolites/minimally excreted unchanged. May aggravate azotemia, Na+ retention, glucose intolerance, and hypertension	100%	100%	100%
Same as earlier	100%	100%	100%
Same as earlier	100%	100%	100%
Same as earlier	100%	100%	100%
Same as earlier	100%	100%	100%
Same as earlier	100%	100%	100%
Same as above	100%	100%	100%
Same as earlier	100%	100%	100%
Same as earlier	100%	100%	100%
Same as above	100%	100%	100%

Comments	HD	CAPD	Continuous Venovenous Hemofiltration
First line, serotonin syndrome risk (antidote cyproheptadine)			
Norfluoxetine is active metabolite with similar activity to parent; activating	None	No data	No data

Continued

TABLE 58.3 Antimicrobial Agents in Adult Patients with Chronic Kidney Disease—cont'd

Antidepressants	Starting Dose	% of Renal Excretion	GFR >60 mL/min	GFR 30–60 mL/min	GFR <30 mL/min
Paroxetine	20 mg/day IR; 25 mg/day ER	2% unchanged	100%	50%	50%
Sertaline	50 mg/day	0% unchanged	100%	100%	100%
Citalopram	20 mg/day	10%	50%	50%	Not recommended for GFR <20 mL/min
SNRIs					
Venlafaxine	37.5 mg/day	5% unchanged	75%	25%	50%
Duloxetine	30–60 mg/day	70%	100%	100%	0% (avoid use)
Others					
Trazodone	50 mg BID (IR) or 150 mg QHS (ER)	75%	100%	50%	100%
Amitriptyline	25–50 mg/day	2% unchanged	100%	100%	100%
Nortriptyline	25 mg/day	2% unchanged	100%	100%	100%
Mirtazapine	15 mg QHS	75%	100%	100%	100%
Bupropion	100 mg BID IR; 150 mg/day (12 hours); 150 mg/day (24 hours)	0.5% unchanged	100%	100%	100%

	Normal Doses		Dosage Adjustment in Renal Failure		
Anticoagulants	Starting Dose	% of Renal Excretion	GFR >50	GFR 10–50 mL/min	GFR <10 mL/min
Alteplase	2 to 100 mg	No data	100	100%	100%
Anistreplase	30 U IV over 2–5 minutes		No data	100%	100%
Aspirin	81 mg/day	325 mg/day	10%	100%	100%
Apixaban	5 mg BID	27	100%	50%	50%
Clopidogrel	LD 300–600 mg, maintenance 75 mg/day	50	100%	100%	100%
Dabigatran	150 mg PO q12h	80	100%	50%	No data
Dalteparin	2500 units SQ/day	Unknown	100	100%	No data
Dipyridamole	75–100 mg QID		No data	100%	100%
Edoxaban	60 mg/day	50	100%	50%	Avoid
Enoxaparin	1 mg/kg q12h	40	100%	100%	50%
Fondaparinux	2.5 mg–10 mg/day		77%	100%	Avoid
Heparin	80 U/kg load then 18 U/kg/h		None	100%	100%
Iloprost	5 µg q15 minutes		68%	100%	100%
Indobufen	100 mg q12h	200 mg q12h	<15%	100%	50%

Comments	HD	CAPD	Continuous Venovenous Hemofiltration
Most anticholinergic, sedating; withdrawal most likely	50%	No data	No data
Good middle start	None	No data	No data
Low DDIs; QTc prolongation	No data	No data	No data
Highest sexual dysfunction	50%	50%	
More neuropathic	Not dialyzable	Unlikely to be dialyzable	Unlikely
For anxiety and insomnia. Use with caution, no renal adjustments per label	No data	No data	No data
Neuropathic properties. Use with caution, no renal adjustments per label. Avoid in cardiac disease and seizure history.	No data	No data	No data
	No data	No data	No data
For cachectic and end-of-life patients. Clearance is decreased with moderate and severe renal impairment. Use with caution.	No data	No data	No data
Augmenting agent; increase seizure risk; avoid in TBI, bulimia, anorexia; abuse potential	No data	No data	No data

Comments	HD	CAPD	Continuous Venovenous Hemofiltration
Patients > 100 kg LD is 9 mg IV bolus over 1 minute, followed by 81 mg continuous infusion over 60 minutes	100%	100%	100%
	100%	100%	100%
	100%	100%	100%
Only reduce dose if two of the three are present: CrCl < 30, weight < 60 kg, and 80 years old	100%	100%	100%
	100%	100%	100%
	Avoid	Avoid	Avoid
	Avoid	Avoid	Avoid
	Avoid	Avoid	Avoid
Monitor Xa Level	Avoid	Avoid	Avoid
Monitor Xa Level		Avoid	Avoid
Monitor Xa level		Avoid	Avoid
		Avoid	Avoid
	Avoid	Avoid	Avoid

Continued

TABLE 58.3 Antimicrobial Agents in Adult Patients with Chronic Kidney Disease—cont'd

	Normal Doses		Dosage Adjustment in Renal Failure		
Anticoagulants	Starting Dose	% of Renal Excretion	GFR >50	GFR 10–50 mL/min	GFR <10 mL/min
Prasugrel	LD 60 mg, maintenance 5–10 mg/day	68	100%	100%	100%
Rivaroxaban	20 mg q24h	20 mg q24h	66%	100%	50%
Streptokinase	1,500,000 IU IV infused over 60 minutes		Unknown	100%	100%
Ticagrelol	LD 180 mg, maintenance 90 BID	26	100%	100%	100%
Ticlopidine	250 mg q12h	60	100%	100%	100%
Urokinase	4400 U/kg load; then 4400 U/kg qh		100%	100%	100%
Warfarin	5 mg/day	1%	100%	100%	100%

ACEI, Angiotensin-converting enzyme inhibitor; *ADHD*, attention deficit hyperactivity disorder; *AKI*, acute kidney injury; *ARB*, angiotensin II receptor blocker; *ARF*, acute renal failure; *ARNI*, angiotensin receptor-neprilysin inhibitor; *ASCVD*, atherosclerotic cardiovascular disease; *ASA*, aspirin; *AUC*, area under the receiver operating characteristic curve; *AV*, arteriovenous; *BBW*, waring box; *BG*, blood glucose; *BID*, twice a day; *BP*, blood pressure; *BUN*, blood urea nitrogen; *CAPD*, continuous ambulatory peritoneal dialysis; *CDAD*, *Clostridium difficile*–associated disease; *CI*, clearance; *CKD*, chronic kidney disease; *CMV*, cytomegalovirus; *CNS*, central nervous system; *COX-2*, cyclooxygenase-2; *CrCl*, creatinine clearance; *CRRT*, continuous renal replacement therapy; *CSA*, cyclosporine; *CV*, cardiovascular; *d/c*, discontinue; *DDI*, drug interactions; *DKD*; *ECG*, electrocardiogram; *eGFR*, estimated glomerular filtration rate; *ER*, Extended Release; *ESRD*, end-stage renal disease; *FLX*, high flex; *GFR*, glomerular filtration rate; *GI*, gastrointestinal; *HA*, headache; *HCTZ*, hydrochlorothiazide; *HD*, hemodialysis; *HDL*, high-density lipoprotein; *HF*, heart failure; *HR*, heart rate; *HSV*, herpes simplex virus; *HUS*, hemolytic uremic syndrome; *IM*, intramuscular; *INR*, international normalized ratio; *IR*, immediate release; *IV*, intravenous; *KDIGO*, Kidney Disease: Improving Global Outcomes; *KF*, kidney function; *LD*, loading dose; *LFT*, liver function test; *MAOI*, monoamine oxidase inhibitors; *MAX*, maximum; *MOA*, mode of action; *MRSA*, Methicillin-resistant *Staphylococcus aureus*; *N/A*, not applicable; *NR*, not reported; *NS*, normal saline; *NSAID*, nonsteroidal anti-inflammatory drug; *N/V*, Nausea, Vomiting; *N/V/D*, Nausea, Vomiting, Diarrhea; *NYHA*, New York Heart Association; *PCN*, Penicillin; *PD*, Peritoneal dialysis; *PO*, orally; *PT*, prothrombin time; *QAM*, every morning; *QD*, every day; *QHS*, at bedtime; *QID*, four times a day; *QOD*, every other day; *RBF*, renal blood flow; *SE*, side effect; *SNRI*, serotonin–norepinephrine reuptake inhibitor; *SQ*, subcutaneous; *SSRI*, selective serotonin reuptake inhibitor; *SSTI*; *TBI*, traumatic brain injury; *TDM*, therapeutic drug monitoring; *TID*, three times a day; *TTP*, Thrombotic thrombocytopenic purpura; *XL*, slow release; *UIT*, units; *VZV*, varicella-zoster virus.

information on drugs that require dosing adjustment for patients with ESKD and on the half-lives of the drugs (hours). The adjustment for ESKD applies to patients with kidney function poor enough to require maintenance dialysis (GFR generally <10 mL/min). In patients with kidney failure, a careful pharmacotherapeutic plan pertinent to each patient's situation should be developed. When the method of adjustment is interval extension (I), the number of hours that should elapse between doses is indicated in Table 58.3. The quantity of the dose should be the same as that given to a patient with normal kidney function. On the other hand, when the dose reduction method (D) is recommended, the adjustment refers to the percentage of the dose given to a patient with normal kidney function. This dose should be given at the usual dosing interval. Table 58.3 indicate the dosage formulation and currently available formulations. However, similar to any clinical guideline, patient-specific factors such as age, disease state, nutrition, and body fluid should be considered during the dosage adjustments.

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Comments	HD	CAPD	Continuous Venovenous Hemofiltration
	Avoid	Avoid	Avoid
	Avoid	Avoid	Avoid
	100%	100%	100%
Reversible antiplatelet	100%	100%	100%
Avoid	100%	100%	100%
Increased risk of bleeding	100%	100%	100%
Monitor INR closely	100%	100%	100%

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Medication Management

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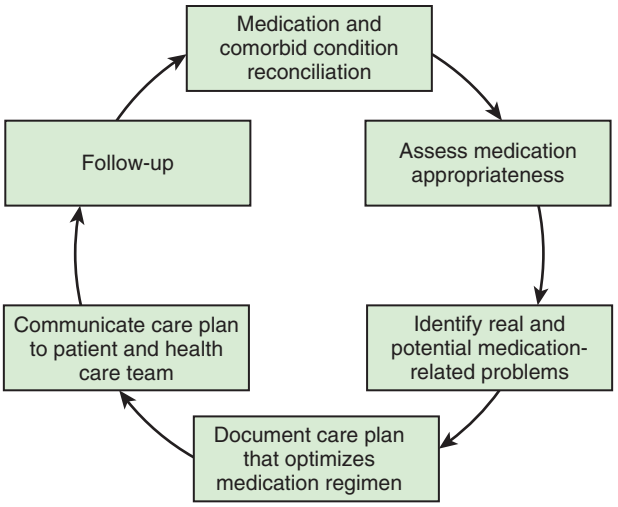
Medication management is a patient-centered care process that optimizes safe, effective, and appropriate drug therapy. Medication management is a repeating process that involves patient assessment, creating and implementing a care plan, and follow-up and evaluation (Fig. 59.1). Care is provided through collaboration with patients and their health care teams, including physicians, nurses, pharmacists, dietitians, social workers, and patient care technicians.

An average dialysis-dependent patient has five or six comorbid conditions, requiring 10 to 12 medications, resulting in an average of 19 pills (range, 17–25 doses) daily. This polypharmacy does not necessarily reflect poor medical management or overuse of medications. However, the sheer number of medications, the presence of kidney altered drug disposition, and the challenges involved with tracking, monitoring, managing, and actually taking all these medications place dialysis patients at high risk for medication-therapy problems (MTPs). In addition to complex polypharmacy, the average dialysis patient also experiences "polyprovider" issues. The typical dialysis patient has nearly five different prescribers (e.g., nephrologist, primary care provider, endocrinologist, cardiologist, gastroenterologist, and psychiatrist) and uses several pharmacies (e.g., mail order, specialty, chain drug store, large retailer, food market, or independently owned pharmacy) to obtain access or afford their medications. In a cross-sectional analysis of Medicare claims data (January 1–December 31, 2016), including over 25,747,560 patients who were 65 years of age or older and who were prescribed at least one medication for at least 30 days were analyzed. Overall, patients had 5.6 (1.1) different prescribers, and mean concurrent medications per patient was 5.6 (range, 1–46; SD, 3.3), and mean number of unique medications per patient was 6.3 (range, 1–59). Fifty-seven percent of patients were prescribed five or more medications. The most significant factor associated with polypharmacy was patient medical complexity, including those with a history of HIV/AIDS, diabetes mellitus, solid organ transplant, or systolic heart failure. In a separate Medicare-managed care study, 405 patients (age, 74 [5.1] years) had a mean (SD) of 2.9 (1.3) prescribing physicians, and 98 (24%) of patients reported having experienced an adverse drug event (ADE) in the previous 6 months. In a multivariable logistic regression model, each additional provider prescribing medications increased the odds of reporting an ADE by 29% (odds ratio [OR], 1.3; 95% confidence interval [CI], 1.0–1.6). The number of chronic health conditions was also associated with ADEs. Having four or five self-reported chronic conditions doubled a person's odds of experiencing an ADE (OR, 2.1; 95% CI, 1.0–4.1), and having six or more conditions tripled the likelihood of experiencing an ADE (OR, 3.4; 95% CI, 1.6–6.9). The number of prescribing physicians was an independent risk factor for patients self-reporting an ADE. The authors suggest that one possibility for higher ADEs is poor communication among multiple providers.

The complex medical management of various comorbid conditions and the fragmented health care system with inadequate communication among multiple prescribers and pharmacies, as well as the frequent care transitions between ambulatory care sites (e.g., dialysis center, ambulatory primary care practice, ambulatory specialty practice) and the hospital, skilled nursing facility, or long-term care facility, places dialysis patients at high risk for MRPs. Previous reports illustrate that risk factors for experiencing MRPs include three or more concurrent disease states, medication regimen changed four or more times during the past 12 months, taking five or more medications or 12 or more doses per day, noncompliance history, drugs that require therapeutic monitoring, and the presence of kidney disease or diabetes as a chronic condition. Dialysis patients have all of these risk factors. Providing medication management services is critically important to avoid adverse clinical events and the high costs associated with MRPs, often resulting in avoidable hospitalizations.

Medication-related problems can be classified into nine categories: (1) indication without drug therapy (IWD); (2) drug without indication (DWI); (3) improper drug selection (IDS); (4) subtherapeutic dosage, that is, (5) underdose (UD), (6) overdosage (OD), (7) or adverse drug reaction (ADR); (8) drug interaction (DI; failure to receive drug [FRD]); and (9) inappropriate laboratory monitoring (LAB). Table 59.1 provides examples for each MRP type.



• **Fig. 59.1** Medication management process.

TABLE 59.1 Medication-Related Problem Definitions

MRP	MRP Abbreviation	Definition
Overdose	OD	An excessive amount of the proper medication is used.
Subtherapeutic dosage	UD	The patient is not receiving enough of the proper medication.
Indication without drug	IWD	The patient could benefit from drug therapy but is not being treated.
Drug without indication	DWI	The patient takes a medication without necessity.
Drug interaction	DI	A drug, disease, or food causes a problem with an existing medication.
Adverse drug reaction	ADR	The patient experiences an untoward effect from a medication.
Improper drug selection	IDS	A condition is treated with a medication other than the drug of choice.
Failure to receive drug therapy	FRD	The patient does not receive the medication that is prescribed (nonadherence, cost, or other issues).
Improper laboratory monitoring	LAB	Laboratory monitoring associated with medication therapy is not done or is inadequate.

MRP, Medication-related problem.

Medication-Related Problems in Dialysis Patients

Most data regarding MRPs in patients with end-stage kidney disease (ESKD) pertain to adults undergoing in-center hemodialysis (HD). Over the past 25 years, many studies have evaluated MRPs in HD patients. A pooled analysis of several studies collectively involving more than 900 patients found the average number of MRPs per patient to be 4.5 (range, 2.8–7.2). For peritoneal dialysis (PD) patients, in a prospective, observational study of 42 patients, the mean number of prescription medications was 9.2, and nonprescription medications were 2.2. Of the patients using antihypertensive agents, 62% used more than one agent, indicating that the medication burden and likelihood of MRPs in PD patients are similar to those of patients undergoing in-center HD.

Pediatric dialysis patients are a subgroup with unique and complex needs regarding medication therapy. These include but are not limited to special dosing (e.g., weight-based), need for compounded pharmaceutical formulations, off-label use of medications, sociodemographic issues extending beyond the patients themselves, and adherence issues. In two observational cohort studies conducted at an inpatient setting and outpatient facility in the United Kingdom, MRPs in pediatric kidney patients were characterized via chart review. Two pharmacists each, having more than 10 years experience in tertiary pediatric kidney pharmacy practice, were involved in collecting the data. A total of 267 MRPs were identified from 266 prescription chart reviews. The incidence of MRPs was 51.2% (203 MRPs, 166 charts; 95% CI, 43.2%–60.6%) in hospitalized patients and 32% (64 MRPs, 100 charts; 95% CI, 22.9%–41.1%) in outpatients. The number of prescribed medications was the only independent predictor during inpatient treatment (OR, 1.06; 95% CI, 1.02–1.10), with no significant predictors identified at outpatient facilities. The severity level of the MRPs was minor, 53.9% (144 of 267), or moderate, 46.1% (123 of 267). Suboptimal drug effect was the predominant MRP (inpatient, 68%; outpatient, 39%). Prescribing errors and patients' medicine-taking behavior were the main contributory factors. The majority of the MRPs in the inpatient setting was resolved.

Another study evaluated the potential scope of MRPs in 283 pediatric patients who made a total of 374 nephrology and hypertension facility visits. Each visit included a pediatric clinical pharmacist team member. The mean number of interventions by the clinical pharmacist was 2.3 on the first visit. These data suggest that focused MRP evaluation by a pharmacist could potentially be valuable in improving total costs and outcomes in pediatric patients with ESKD.

Identifying and Resolving Medication-Related Problems in Dialysis Patients

Medication management, also called medication therapy management (MTM), is a patient-centered process to create treatment plans centered on each patient's

medication-related goals. There are two distinct components to medication management: medication reconciliation and medication review. These two distinct processes are focused on preventing and resolving various MRPs.

1. **Medication and medical problem reconciliation** is the process of creating and maintaining an accurate medical problem and medication list that reflects all current active medical problems and medications that the patient is taking and how they are being taken.
2. **Medication review** is the service whereby a clinician evaluates the medication list for appropriateness, effectiveness, safety, and convenience in conjunction with the patient's health status.

Medication Reconciliation

Clinicians need to be aware of what medication regimen(s) a patient is currently taking or previously exposed to before initiating new or modifying existing medication therapy (i.e., medication reconciliation). Therefore, medication reconciliation could be considered the foundation or primary function to be performed before any clinical intervention is implemented. The goals of medication reconciliation are to identify medication list discrepancies and create the most accurate medication list for patient and health care provider use. Having an accurate medication list provides valuable information to clinicians as they make care management decisions (i.e., medication review process).

Regulatory requirements to perform periodic medication reconciliation in dialysis patients do exist. Since 2008, the Centers for Medicare & Medicaid Services (CMS) Conditions for Coverage has required that a dialysis patient's comprehensive plan of care include a medication history and should be developed within 30 days of patient admittance to a dialysis facility, *at least annually* for stable patients and *monthly* for unstable patients, defined as extended hospitalization (> 15 days), frequent hospitalizations (more than three episodes within 30 days), marked deterioration in health status, significant change in psychosocial needs, concurrent poor nutritional status, unmanaged anemia, or inadequate dialysis. Furthermore, medication history is a component of the Measures Assessment Tool. Codified via V506, it states that "medication history" should include a review of the patient's allergies and of all medications, including over-the-counter (OTC) medications and supplements that the patient is taking. The assessment should demonstrate that all current medications were reviewed for possible adverse effects, interactions, and continued need. Medication reconciliation will be included in the Medicare Quality Improvement Program Safety Domain beginning 2022. U.S. dialysis facilities will be required to attest to providing monthly medication reconciliation on all dialysis patients having more than seven treatments provided in the unit that reporting month. Eligible individuals to perform medication reconciliation include physicians, registered nurses, advanced registered nurse practitioners (ARNP), physician assistants, pharmacists, or pharmacy technicians. Evidence from other clinical settings suggests that pharmacists provide more comprehensive medication reconciliation than physicians. The measure requires dialysis organizations to provide medication reconciliation on a monthly basis using qualified personnel.

Under the medication reconciliation reporting measure, dialysis facilities will have to attest that four items were addressed and documented during the calculation month: (1) the patient's most recent medication list in the dialysis medical record was reconciled to one or more external list(s) of medications obtained from the patient/caregiver (including patient/caregiver provided "brown-bag" information, pharmacotherapy information network, hospital, or other health care provider) and (2) all known medications (prescriptions, over-the-counter medications, herbals, vitamin/mineral/dietary [nutritional] supplements, and medical marijuana) were reconciled. Each medication will also need the following information recorded: medication name, indication, dosage, frequency, route of administration, start and end date (if applicable), discontinuation date (if applicable), reason medication was stopped or discontinued (if applicable), and identification of the individual who authorized stoppage or discontinuation of medication. All patient medication allergies, intolerances, and ADEs will also need to be recorded. Of the medication-related data elements, "Unknown" is an acceptable response for all except "medication name."

Under this reporting measure, CMS will determine the percentage of patient months for which medication reconciliation was performed and documented by eligible professionals. During measure testing, the mean percentage of patients having had medication reconciliation was 52.6% ± 32.8% (median, 48.2%; range, 0%–100%; interquartile range [IQR], 27.6%–87.8%). Although a specific goal is not yet known, a high percentage is desired. The data sources used to calculate percentage of patient months with medication reconciliation will be the Consolidated Kidney Operations in a Web-Enabled Network (CROWNWeb), which is the ESKD National Patient Registry and Quality Measure Reporting System for CMS, facility medical records, and administrative data. In January 2020, CROWNWeb medication reconciliation data reporting began for all HD and PD patients. Dialysis facilities are not required to report the data; however, the system provides users with the ability to review the medication reconciliation fields in preparation for data reporting.

Medication reconciliation is an important patient safety initiative to prevent various MRPs. Medication reconciliation is preparatory to any medication assessment or review, care planning, and evaluation. Given the complex pharmacotherapy regimens, multiple prescribers, utilized pharmacies, and frequent care transitions at each dialysis treatment, patients should be asked if they had any additions, deletions, or changes to their medication lists. The medication list should include all prescribed medications, OTC products, vitamins, and herbal products. Medication reconciliation should occur each time a dialysis patient presents for dialysis by a member of the dialysis center's interdisciplinary

team. Complete medication reconciliation should occur at periodic intervals (e.g., monthly or bimonthly) but at a minimum with each short-term care plan and after transitions in care. Accurate medication reconciliation does require training, and, ideally, a pharmacist would provide this function or specifically train other members of the dialysis team to do so.

Management of an accurate medication list in dialysis patients is complex because of the high medication and pill burden and the involvement of multiple prescribers. In addition, this population experiences nearly two hospitalizations per year. The Institute for Healthcare Improvement, Institute of Safe Medication Practices, and The Joint Commission all recognize that gaps in medication knowledge occurring during transitions of care are responsible for up to 50% of medication errors in the hospital and up to 20% of ADEs. In a small single-center study, 65% of MRPs identified in hospitalized dialysis patients were associated with gaps in transfer of medication information among the patients, caregivers, and various health care settings and caregivers. Similarly, in the general population, discrepancies in medication lists generated from comprehensive patient interviews and physician-acquired medical history were reported in up to 67% of cases at the time of admission to the hospital.

Medication discrepancies can be classified into four groups: no-longer taking (i.e., patient is no longer taking a medication that clinicians thought they were), not in the record (i.e., patient is taking a medication that the clinician was not aware of), dosing issue (i.e., patient is taking a different dose than the clinician thought they were taking), and direction issue (e.g., patient is taking correct dose but at a different frequency than that the clinician thought they were). Medication list discrepancies place dialysis patients at risk for five of the nine MRPs: patient receiving incorrect medication dose (e.g., OD or UD), patient not getting necessary medications (e.g., FRD), patient not getting correct dosage form (e.g., IDS), and patient experiencing an ADE because of unnecessary drug exposure.

Since 2003, several studies worldwide have demonstrated medication discrepancy prevalence and type observed in dialysis patients. Overall, they illustrate that, on average, two to three (range, 1.3–3.9) medication discrepancies can be identified each time a dialysis patient has their medications reconciled. The most common medication discrepancy types are "medication no longer taken" and "medication not in record."

Dialysis facilities often provide patient medication lists to the emergency department or hospitals whenever the patient is admitted; therefore, a dialysis facility's medication list serves as a very important clinical document. Assuming that two to three medication discrepancies are found whenever a dialysis patient has medication reconciliation, extrapolating this to the entire U.S. population of HD (n = 468,086) and PD (n = 52,718) patients suggests that approximately 1 million to 1.6 million medication discrepancies could be identified. It is estimated that 4%–6% of medication discrepancies are clinically relevant and place patients at risk for harm. Therefore, the U.S. dialysis population has an estimated 41,664–93,744 clinically significant medication discrepancies that could cause patient harm.

Two studies highlight the risk related to medication discrepancies for dialysis patients. One study of adults hospitalized via the emergency department found that 97 of 832 patients (11.7%) had at least one medication discrepancy; the most common discrepancies were incorrect medication dose (44.9%) and not in the record (36.4%). Characteristics independently associated with medication discrepancies were age (OR, 1.02; 95% CI, 1.01–1.03) and medication count (OR, 1.10; 95% CI, 1.06–1.15), highly relevant to increasing age and polypharmacy common in the U.S. dialysis population. Another report of 47 dialysis patients admitted to the hospital over a 12-week period identified that 92% of patients with ESKD had at least one medication-related problem at admission (total of 199 distinct issues). The authors determined that 130 (65%) of those issues were related to "gaps in medication information transfer" (i.e., medication discrepancy), most frequently between the inpatient hospital and the ambulatory facility pharmacists (21.5% of the time) and between the admitting physician and the patient (17.7% of the time). Overall, these findings suggest that dialysis patients are at high risk of medication discrepancies. There is a need for high-quality medication reconciliation in dialysis facilities to minimize these discrepancies and subsequent communication of the updated patient medication lists to other care settings.

Over the 5-month period, 215 drug interviews were conducted in 63 patients. A total of 113 drug record discrepancies were identified in 38 patients (60%). Discrepancies (mean ± SD, 1.7 ± 1.3; range, 1–7) were identified during 65 drug interviews (30.2%). Electronic drug records were discrepant by one drug record, two drug records, and more than two drug records 60.0%, 26.2%, and 13.8% of the time, respectively. Medication record discrepancies placed patients at risk for ADEs and dosing errors in 49.6% and 34.5%, respectively, of 113 discrepancies.

In a larger, more recent publication, patients at an academic HD unit were interviewed to obtain the best possible medication history in which medication discrepancies were identified, classified, and resolved with the multidisciplinary team. The team also evaluated discrepancy clinical impact assessment for potential ADEs. A total of 228 patients on HD were interviewed, and 512 discrepancies were identified for 151 patients (3.4 discrepancies per patient). Of these, 174 (34%) were undocumented intentional discrepancies, and 338 (66%) were unintentional discrepancies. The unintentional discrepancies were classified as 21% omissions, 36% commissions, and 43% incorrect dose/frequency. Most medication discrepancies were related to a patient taking a medication that was not indicated (25% and risk for ADE), medication required but patient not taking (25% and risk for FRD), patient not willing to take the medication as prescribed (28% and risk for FRD), or incorrect dosing of a drug (20% and risk for OD or UD). Overall, 6% of discrepancies were classified as clinically significant potential ADEs.

Current barriers to providing comprehensive medication reconciliation in most dialysis facilities in the United States include lack of staff training on the importance and process of medication reconciliation, nonexistent or poor interfaces in electronic health information among care facilities (outpatient dialysis center, hospital, skilled nursing facilities, rehabilitation centers), and the absence of clinical pharmacists in most dialysis facilities.

A consistently applied medication reconciliation process that occurs regularly in the dialysis facility as well as during care transitions could address many of these issues. The medication reconciliation is a person-to-person interaction between a patient (or caregiver) and a health care professional that includes:

- Collection of an accurate list of all medications the patient is taking.
- A comparison between the new medication list and the previous list in the medical record.
- Reconciliation of medications and resolution of any noted discrepancies.

Medication Review

It is important to understand the difference between medication reconciliation and medication review. *Medication reconciliation* is the process whereby an accurate medication list can be constructed and maintained. *Medication review* is the process whereby the patient's medication regimen is evaluated for appropriateness and safety, and it requires advanced clinical pharmacotherapy skills to assess drug therapy in the context of the individual patient's comorbidity, health literacy, and sociodemographic issues (Table 59.2).

Medication review is a multistep process whereby a clinician:

1. Identifies all real and potential MRPs in a patient through clinical assessment of the patient's medical conditions, medications taken, and other available clinical data (e.g., laboratory results, physical exam).
2. Creates and documents a plan of care to resolve or prevent MRPs identified to optimize therapeutic outcomes associated with patient's medication use.
3. Communicates any change(s) to the patient's medication regimen to the patient and their care providers.
4. Educates patients regarding any change(s) to therapy.

In a 2-year randomized controlled trial of 104 HD patients assigned to receive pharmaceutical care (in-depth bimonthly medication therapy reviews conducted by a clinical pharmacist) or usual care (brief medication therapy reviews conducted by nurse), the former was associated with fewer hospitalizations (1.8 ± 2.4 vs. 3.1 ± 3; $p = 0.02$); the trend for reduced length of stay did not achieve statistical significance (9.7 ± 14.7 vs. 15.5 ± 16.3 days; $p = 0.06$). A recent study showed that integrated pharmacy services in HD patients receiving Medicare and Medicaid were associated with lower rates of death and hospitalization. Program services were deployed over time and included medication reconciliation and review at the time of program enrollment, as well as medication delivery and refill management. In addition, patients had round-the-clock access to pharmacists who provided telephonic medication management services. Future studies are needed to measure patient utilization of various pharmacy services and outcomes associated with that utilization. In a retrospective cohort study of maintenance dialysis patients discharged home from acute care hospitals, patients who received MTM services consisting of nurse medication reconciliation, pharmacist medication review, and nephrologist engagement had lower time-varying 30-day readmission risk (Hazard ratio [HR], 0.26; 95% CI, 0.15–0.45) versus those who did not receive MTM. In a propensity score-matched sensitivity analysis, MTM services continued to be associated with lower 30-day readmission risk (HR, 0.20; 95% CI, 0.06–0.69).

The Medicare Modernization Act of 2003 created the provision for prescription drug coverage for Medicare beneficiaries through Medicare Part D. Within that provision, Medicare prescription drug plans are mandated to provide MTM services to "high-risk enrollees" who meet various eligibility requirements. Eligible beneficiaries for MTM services are enrollees in a specific Part D plan who meet *all* of the following: (1) have multiple chronic diseases, (2) are taking multiple Part D drugs, and (3) are likely to incur $ 4255 or more annual Part D drug costs in 2020 and subsequent years (drug cost threshold specified by CMS §423.153(d)(1)).

TABLE 59.2 Comparison Between Medication Reconciliation and Medication Review

Medication Reconciliation Process	Medication Review Service
1. Collection of an accurate list of all medications the patient is taking	1. Identifies all real and potential MRPs in a patient through clinical judgment of patient's medical conditions, medications taken, and other available clinical data (e.g., laboratory results, physical exam)
2. Comparison between new medication list and previous list in the medical record	2. Creates and documents a plan of care to resolve or prevent MRPs identified in order to optimize therapeutic outcomes associated with patient's medication use
3. Reconciliation of medications and resolution of any noted discrepancies	3. Communicates any change(s) to the patient's medication regimen to the patient and his or her care providers
	4. Educates patient regarding any change(s) to therapy

MRP, Medication-related problem.

Medicare requires pharmacist involvement in MTM program creation and allows Part D MTM program services to be provided by pharmacists or other qualified providers. In 2019, all Part D MTM programs used pharmacists to provide the services. Physicians and registered nurses were allowed by health plans to provide MTM services 24.5% and 74% of the time, respectively.

In providing MTM services, the provider will work with the member and physician or other caregivers to establish and achieve drug therapy treatment goals, avoid or minimize undesirable medication effects, and improve clinical outcomes. Additionally, the plan is patient-centric and a comprehensive approach to improve medication use, reduce the risk of adverse events, and improve medication adherence.

Medicare also mandates that every targeted patient who meets Part D plan criteria for MTM be offered a complete medication review that is documented in a standard format. The Medicare MTM Program Standardized Format (Format) is a written summary of a comprehensive medication review (CMR). A CMR is an interactive person-to-person or telehealth medication review and consultation conducted in real time between the patient or other authorized individuals, such as prescriber or caregiver, and the pharmacist or other qualified provider. The CMR is designed to improve patients' knowledge of their prescriptions, OTC medications, herbal therapies, and dietary supplements; identify and address problems or concerns that patients may have; empower patients to self-manage their medications and health conditions. The pharmacist or qualified provider must assess a patient's medication therapy and create a plan to optimize patient outcomes. Section 10328 of the Affordable Care Act amended section 1860D-4(c)(2)(ii) of the Act to require prescription drug plan sponsors to offer, at a minimum, an annual CMR and required the development of a standardized format for the action plan and summary. Standardization of the format of these documents is expected to improve the quality of the MTM program services and provide consistency in beneficiary communications across differing Medicare Part D programs.

After each interactive CMR, the patient is provided an individualized written "take-away" that includes a personal medication record, reconciled medication list, and medication action plan that includes recommendations for monitoring, education, or self-management. The medication action plan contains specific patient and provider recommendations to address any MRPs identified. The patient's provider also receives a copy of the medication action plan for their consideration.

In addition to CMRs, Medicare requires targeted medication reviews (TMRs) to occur at least quarterly in all eligible patients. A TMR may be an interactive person-to-person medication review and consultation but may be delivered via the mail or other means. TMRs should occur at least quarterly and after a sentinel event (e.g., transitions of care, fall event) and are used to assess current medication use, identify unresolved MRPs from the annual CMR, identify new MRPs, and identify patients who have had a transition in care or hospitalization. After each follow-up TMR, a new medication action plan may be created and provided to the patient or provider(s) (or both).

Despite the various efforts to increase patient MTM eligibility and minimum provider requirements for MTM services, there remains significant heterogeneity among the various Part D prescription drug plans regarding patient selection criteria, provider type (e.g., nurse versus pharmacist), and the level of care (e.g., telephone vs. person to person). Approximately 77% of eligible Medicare Part D beneficiaries actually obtain MTM services.

Nearly all dialysis patients would be eligible for MTM services because their per-beneficiary per-year medication costs (Parts B and D combined) far exceed the $4255 threshold to qualify for MTM services. In 2016, ESKD patients' spending for medications was 4.1 times higher than the general Medicare population ($13,310 vs. $3559). Dialysis patients receive prescription medications from multiple pharmacies (e.g., dialysis organization pharmacy, community pharmacy, mail order pharmacy), further fragmenting medication management services. For many community pharmacists, the only indication that a patient has kidney disease or is dialysis dependent has often been the presence of a phosphate binder or cinacalcet in the medication profile. When these medications are no longer filled by a patient's community pharmacist, MRPs such as necessary dosage adjustments of other medications may not be identified at the time the prescription is dispensed. Providing medication management services in conjunction and alignment with dialysis services is essential to overcome these challenges.

The dialysis facility can serve as the central medication coordination center and the dialysis health care team as the medication coordination team for each patient. The dialysis facility is the most logical and convenient location for integrated pharmacy services, including medication pick-up, medication reconciliation, and person-to-person medication management services, to occur. This is also a model that could be used by home dialysis patients who make trips to the dialysis center for routine care. Including a clinical pharmacist as an integral part of the dialysis facility team to help provide these medication-related services within the construct of the existing team would substantially facilitate medication management services. In Canada, clinical pharmacy services fund one pharmacist per 100 HD patients, 200 peritoneal or home HD patients, and 300 chronic kidney disease (stages 3–5) patients and have been shown to reduce costs and improve clinical outcomes. Although the structure and costs of the Canadian health care system differ from those in the United States, these data suggest pharmacist-to-patient ratios that are successful in impacting patient outcomes.

Economic Impact

Identification and resolution of MRPs will result in improved patient outcomes and reduced health care expenditures. Reducing MRPs has the potential to generate considerable cost savings for the health care system. It has

been estimated that for every $1 spent on detecting and addressing MRPs in the dialysis population, $4 may be saved by the health care system. These cost savings are expected to accrue by lower prescription drug costs from avoidance of unnecessary or inappropriate medications and fewer hospitalizations. A sustainability model could be developed that uses a portion of net savings from Medicare Part A, which could support medication management services under Medicare Part B, using available data regarding reduced hospital admissions and lengths of stay. Indeed, MRPs in the general population are implicated in approximately 16% of hospital admissions, and 50% of these hospitalizations are potentially avoidable. In one report involving patients with chronic kidney disease stage 5, medications were implicated in nearly 50% of hospitalizations, considered the sole reason for admission 18% the of time, and considered a contributor but not the sole cause for the admission 29% the of time. Another report found that nearly 50% of MRPs identified in dialysis patients admitted to the hospital were preexisting, and another 50% occurred during hospitalization (26.7%) or at discharge (25.5%).

The current Medicare ESKD prospective payment system does not include the resources to establish and maintain a model of patient care that includes comprehensive medication management services. As health care models are evolving in the general population, there is an opportunity to design and assess innovative models of care in dialysis patients in collaboration with practitioners, dialysis providers, and CMS. Establishing comprehensive medication management services, including face-to-face review by a pharmacist and regularly scheduled medication reconciliation for all dialysis patients, would necessitate compensation for these services.

Providing medication management services could increase revenue at the facility level. Facilities with medication management services may have lower hospitalization rates and, thereby, fewer missed dialysis treatments. Additionally, approved Current Procedural Terminology (CPT) codes for MTM exist (99605, 99606, 99607), and medication management services could be covered by billing under these codes at standard reimbursement rates. Presently, there is no standard reimbursement rate for each CPT code. Different payers, such as Part D prescription drug plans (PDPs) or commercial health care plans, establish their own payment guidelines and rates for services on a plan-to-plan basis. Reimbursement rates vary based on complexity of medication review and time spent conducting the medication review.

As previously mentioned, CMS requires Part D PDPs to provide MTM services for high-risk, high-cost patients. Data also suggest that dialysis staff believe medication management services are needed and valuable. CMS should encourage programs to develop strategic programmatic growth through cost-sharing mechanisms that would allow dialysis organizations to offset additional costs of comprehensive medication management services by sharing in any potential cost reductions (e.g., reduced hospitalizations and facility visits). The Affordable Care Act created the CMS Innovation Center to test payment and service delivery models, reduce costs, and improve quality. CMS partnered with dialysis organizations to form ESKD Seamless Care Organizations (ESCOs) to test and evaluate a new model of payment and care delivery specific to Medicare beneficiaries with ESKD. Participating ESCOs are clinically and financially responsible for all care offered to a group of matched beneficiaries, not only dialysis care or care specifically related to a beneficiary's ESKD. Medication management was a required component of the ESCOs, and MTM program results demonstrated lower time-varying 30-day readmission risk in dialysis patients that received MTM versus those that did not receive MTM. The impact of the MTM program on savings from a reduction in total costs of care (resulting from, for instance, reduced hospitalizations) is not known.

Conclusion

Dialysis patients have complex medication regimens with large pill burdens, use multiple prescribers and pharmacies, and experience many care transitions. MRPs frequently occur in dialysis-dependent patients and are associated with poor outcomes and high costs. Systematic provision of medication management will identify and resolve MRPs and will likely improve patient outcomes and reduce total cost of care.

Recommended Reading

2019 Medicare Part D medication therapy management (MTM) programs: fact sheet summary of 2019 MTM programs https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/CY2019-MTM-Fact-Sheet.pdf.

Illustrates the overall characteristics of MTM programs provided to Medicare beneficiaries during 2019.

Agency for Healthcare Research and Quality. Centers for Medicare & Medicaid Services (CMS) End-Stage Kidney Disease quality Incentive Program (ESKD QIP) payment year (PY) 2022 measure technical specifications. June 5, 2019. https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/ESKDQIP/Downloads/PY-2022-Proposed-Rule-Technical-Specifications.pdf

Detailed description of Medicare requirements for medication reconciliation at dialysis facilities.

Cardone KE, Bacchus S, Assimon MM, Pai AB, Manley HJ. Medication-related problems in CKD. *Adv Chronic Kidney Dis.* 2010;17(5):404–412.

This is a systematic and detailed review of on the prevalence and effect of medication-related problems in chronic kidney disease patients, including dialysis.

Chan WWY, Mahalingam G, Richardson RMA, Fernandes OA, Battistella M. A formal medication reconciliation programme in a haemodialysis facility can identify medication discrepancies and potentially prevent adverse drug events. *J Ren Care.* 2015;41(2):104–109.

Illustrates medication reconciliation program can reduce medication discrepancy–related and medication-related problems.

Centers for Medicare & Medicaid Services. Comprehensive ESKD Care initiative. <http://innovation.cms.gov/initiatives/comprehensive-ESKD-care/>. Accessed 01.07.15.

Description of the Comprehensive ESKD Care initiative as the first disease-specific Accountable Care Organization model designed by CMS to identify, test, and evaluate new ways to improve care delivery and payment for Medicare beneficiaries with ESKD.

Centers for Medicare & Medicaid Services. CY. Medication Therapy Management Program guidance and submission instructions. *April.* 2020;5:2019. https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Memo-Contract-Year-2020-Medication-Therapy-Management-MTM-Program-Submission-v-041019-.pdf.

A detailed description of Medicare requirements for medication therapy management eligibility and additional program requirements for calendar year 2020.

Centers for Medicare & Medicaid Services. Prescription Drug Benefit Manual, Chapter 7, Medication Therapy Management and Quality Improvement Program. <http://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Chapter7.pdf>; Accessed 21.07.15.

Detailed description of Medicare program requirements for medication therapy management services.

Green JL, Hawley JN, Rask KJ. Is the number of prescribing physicians an independent risk factor for adverse drug events in an elderly outpatient population? *Am J Geriatr Pharmacother.* 2007;5(1):31–39.

Illustrates that multiple prescribers and multiple chronic conditions are independent risk factors for ADE occurrences.

Ibrahim N, Wong IC, Patey S, et al. Drug-related problem in children with chronic kidney disease. *Pediatr Nephrol.* 2013;28(1):25–31.

Illustrates the prevalence of medication-related problems in pediatric patients with kidney disease, including dialysis.

Manley HJ, Aweh G, Weiner DW, et al. Multidisciplinary medication therapy management and hospital readmission in patients undergoing maintenance dialysis: a retrospective cohort study. *Am J Kidney Dis.* 2020;76(1):13–21.

Illustrates that medication therapy management services including medication reconciliation and medication review is associated with lower 30-day readmission risk in dialysis patients.

Manley HJ, Carroll C. The clinical and economic impact of pharmaceutical care in end-stage kidney disease patients. *Semin Dial.* 2002;15:45–49.

Identifies the economic impact associated with resolving medication related problems in dialysis patients.

Manley HJ, Drayer DK, McClaran M, Bender W, Muther RS. Drug record discrepancies in an outpatient electronic medical record: frequency, type, and potential impact on patient care at a hemodialysis center. *Pharmacotherapy.* 2003;23:231–239.

First report illustrating that medication record discrepancies in dialysis patients contribute to medication-related problems.

Ellenbogen ML, Wang P, Overton HN, et al. Frequency and predictors of polypharmacy in US Medicare patients: a cross-sectional analysis at the patient and physician levels. *Drugs & Aging.* 2020;37:57–65.

Illustrates that Medicare beneficiaries a have several comorbidities contributing to polypharmacy and multiple providers.

Ong SW, Fernandes OA, Cesta A, Bajcar JM. Drug-related problems on hospital admission: relationship to medication information transfer. *Ann Pharmacother.* 2006;40:408–413.

Illustrates the complex and fragmented health care system and how it contributes to medication-related problems and hospitalizations in dialysis patients.

Pai AB, Cardone KE, Manley HJ. et al; Dialysis Advisory Group of American Society of Nephrology. Medication reconciliation and therapy management in dialysis-dependent patients: need for a systematic approach. *Clin J Am Soc Nephrol.* 2013;8(11):1988–1999.

Thorough review of available evidence and recommendations for optimal delivery of medication management services to ESKD patients in a dialysis facility–centered model.

Weinhandl ED, Arneson TJ, St. Peter WL. Clinical outcomes associated with receipt of integrated pharmacy services by hemodialysis patients: a quality improvement report. *Am J Kidney Dis.* 2013;62(3):557–567.

Illustrates that integrated dispensing and clinical pharmacy services reduces hospitalization and mortality rates in dialysis patients.

Van Der Luit CD, De Jong IR, Ebbens MM, et al. Frequency of occurrence of medication discrepancies and associated risk factors in cases of acute hospital admission. *Pharm Pract (Granada).* 2018;16(4):1301.

Illustrates that medication discrepancies directly contribute to hospital admissions.

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Physical Activity, Function, and Exercise-Based Rehabilitation for People on Dialysis

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Introduction

The focus on increasing physical activity for those people with a high burden of cardiometabolic) conditions and complications (i.e., kidney failure, diabetes, cardiovascular comorbidities) for managing symptoms and maintaining physical well-being is at an all-time high. Rehabilitation, meaning recovering or restoring what is necessary to get on with living, has been a low priority in most dialysis facilities, and the inclusion of integrated rehabilitation programs for dialysis patients is not routinely offered as part of patient care. The Kidney Disease Outcomes Quality Initiative (KDOQI) practice guidelines for physical activity states that all dialysis patients should be counseled and regularly encouraged by nephrology and dialysis staff to increase their level of physical activity. Please refer to KDOQI guideline 14: "Smoking, Physical Activity, and Psychological Factors."[1]

A published British Association of Sport and Exercise Science (BASES) expert statement in 2015 on exercise for people with chronic kidney disease (CKD) suggests that every stable patient with CKD, irrespective of age, gender, comorbidities, or prior exercise experience, should be provided with specific written advice on how to safely and effectively increase physical activity to (i) enhance confidence and self-efficacy in performing physical activities; (ii) attenuate deterioration of physical function and associated limitations in activities of daily living (ADLs); (iii) increase physiological reserve; (iv) reduce comorbid events; and (v) enhance quality of life (QOL).[2] The focus of this chapter is on the core principle of exercise for reversing the effects of physical deconditioning and optimizing physical functioning and QOL in patients on dialysis.

Definitions

Physical function is often used as a term to encompass many concepts. Physical function is best defined as an individual's ability to perform activities required in their daily life. Physical functioning is determined by many factors, including physical fitness (cardiorespiratory fitness, strength, and flexibility), sensory function, clinical condition, environmental factors, and behavioral factors. *Physical fitness* is a set of attributes people have or achieve that relates to the ability to perform physical activity. One of these attributes is *cardiorespiratory fitness* (often referred to as *exercise capacity*), which relates to the ability of the cardiac, circulatory, and respiratory systems to supply and use oxygen during sustained physical activity.

Physical functioning can be improved with regular physical activity or exercise training. *Exercise* (physical activity) is defined as bodily movement produced by the contraction of skeletal muscle that substantially increases energy expenditure. *Exercise training* is planned, structured, and repetitive bodily movement done to improve or maintain one or more components of physical fitness or to obtain other health benefits. Increased *physical activity* can be considered exercise training, although increased physical activity can also result from

TABLE 60.1 Definition of Terms Related to Physical Function

- *Physical function:* an individual's ability to perform activities required in daily life
- *Physical fitness:* a set of attributes that relates to the ability to perform physical activity (e.g., cardiorespiratory fitness, muscle strength, flexibility)
- *Exercise capacity (cardiorespiratory fitness):* attribute that relates to the ability of the cardiac, circulatory, and respiratory systems to supply and use oxygen during sustained physical activity
- *Exercise (physical activity):* bodily movement produced by muscle movement that substantially increases energy expenditure
- *Exercise training:* planned, structured, and repetitive bodily movement done to improve physical fitness or to obtain other health benefits

unstructured increases in movements throughout the day. The use of the term *physical activity* may be less intimidating to dialysis patients who are typically elderly and often frail or chronically fatigued. However, exercise training is appropriate and recommended for dialysis patients due to their extremely low levels of physical functioning and exercise capacity. Table 60.1 outlines these definitions.

Physical Activity and Function

Physical inactivity is associated with a significantly higher risk of premature morbidity and mortality and poorer QOL outcomes in people requiring hemodialysis (HD).[3,4] There is an increased age profile of incident patients on HD, with a median age of 65 years, and an associated presence of the clinical syndrome of frailty.[5] This syndrome is characterized by persistent fatigue, weight loss, muscle weakness, severe functional limitations, and low physical activity levels, many of which often deteriorate further as time on dialysis increases. This translates into an impaired capacity to undertake ADLs and to live independently and to impaired QOL.[6] Physical function, regardless of how it is measured, is low in patients at all stages of CKD.[7] Higher levels of physical function and habitual physical activity have been shown to be related to enhanced longevity, less morbidity, lower hospitalization rates, and enhanced QOL, in patients receiving dialysis-based kidney replacement therapy.[8–10]

Exercise Rehabilitation

Exercise rehabilitation has started gaining some attention as an appropriate and safe option to improve physical function, which is an integral component of physical independence and QOL, by aiming to alleviate muscle weakness/dysfunction and maintain adequate cardiorespiratory fitness and thus impact on less cardiovascular morbidity and mortality. Physical inactivity is a modifiable risk factor, and exercise interventions designed to increase physical activity and fitness components and reduce sedentary behaviors in patients at risk of cardiovascular disease may improve health-related outcomes and be cost effective in the longer term.[4,11] A recent report of practice-based evidence[12] that incorporated a multicomponent exercise rehabilitation program in clinical patient care path for people in all stages of CKD revealed that people who completed the program and improved fitness had a significantly longer cardiovascular event-free survival time over an observation period of 34 months.[12]

HD therapy enforces regular sedentary behavior three times a week, for up to 4 hours at a time. A main facilitator to intradialytic exercise would, therefore, be the reduced time and transport cost burden to patients as exercise time can be incorporated during dialysis therapy. There is also the potential for an improvement in dialysis efficiency and enhanced solute removal.[13,14] Current understanding of UK-based practices indicates that provision of physical activity/exercise programs for patients with CKD appears to be extremely varied across the UK and is often only an option for patients in an area where research studies are being conducted.[15] There are now 15 published systematic reviews and meta-analyses that have evaluated the overall effectiveness of exercise interventions on various health-related outcomes in patients from all stages of CKD and following transplantation[16,17] and in patients on HD only.[18–31] Koufaki et al.[32] published a systematic review and synthesis of the research evidence in an attempt to translate the findings from these systematic and meta-analytic reviews, together with any recently published research evidence, to provide some well-informed recommendations on exercise rehabilitation in CKD. The reader is directed to these published reviews for an in-depth analysis of the research literature. Some of the associations of physical function and clinical outcomes in dialysis patients are outlined in Table 60.2.

Physical Function Assessment for People with Chronic Kidney Disease

In light of the strong associations between physical function limitations, muscle weakness, physical activity levels, and adverse health outcomes,[9,10] physical function

TABLE 60.2 Studies Relating Physical Functioning and Physical Activity to Outcomes

Measure	Findings	Citation
VO_{2peak}	VO_{2peak} < 17.5 mL/kg/min had greater deaths compared to VO_{2peak} > 17.5 mL/kg/min. Exercise capacity was the strongest predictor of survival over the 3.5-year follow-up.	Sietsema K, et al. *Kidney Int.* 2004;65:719–724.
Self-reported function	Patients with PCS score (SF-36) below the median (<34) were twice as likely to die and 1.5 times more likely to be hospitalized. For every 5-point increase in the PCS, there was a corresponding 10% increase in the probability of survival.	De Oreo P. *Am J Kidney Dis*. 1997;30:204–212
	Compared with patients with a PCS score (SF-36) > 50, those with PCS score < 20 had a hazard ratio of 1.97; those with PCS of 20–29 had a hazard ratio of 1.62; and those with a PCS score of 30–39 had a hazard ratio of 1.32. A decline in PCS over 1 year resulted in additional mortality and increased risk of mortality: hazard ratio of 1.25 per 10-point decline in PCS score.	Knight, et al. *Kidney Int*. 2003;63:1843–1451.
	PF scale on Duke Health Profile was predictive of survival: a difference of 10 points results in 63% greater chance of survival over 1 year.	Parkerson, et al. *Health Care Financing Rev*. 2001;21:171–184.
Physical activity (from USRDS wave 2 form)	Patients who were sedentary at study initiation of dialysis had a 62% greater risk of mortality over 1 year compared with nonsedentary patients.	O'Hare A, et al. *Am J Kidney Dis*. 2003;41:447–454.
	Mortality risk was lower for patients who exercised two to three times per week (RR, 0.74) or four to five times per week (RR, 0.70).	Stack A, et al. *Am J Kidney Dis*. 2005;45:690–701.

PCS, Physical composite score; *RR*, Relative reliability; *SF-36*, Short Form 36; *USRDS*, U.S. Renal Data System.

outcomes should be measured routinely as part of initial and ongoing dialysis patient assessment (BASES statement). The choice of assessment tools will largely be determined by the individual patient's overall health status and willingness to collaborate and staff expertise and equipment availability (as majority of physiological function tests require expensive and technically sophisticated devices). It is also important to note that for some patients, physical function/functional capacity assessment and especially the determination of peak exercise capacity may be contraindicated, such as in cases of uncontrolled coexisting medical conditions/infections, unstable on dialysis treatment with large fluctuations in body mass, blood pressure (BP), etc. Furthermore, the choice of type and specific protocol for physical function assessment should be based upon the primary purpose of the assessment (diagnostic, exercise training prescription, risk stratification, etc.) and should also take into consideration the specific characteristics of the tests available (e.g., validity, reproducibility, and availability of normative data). Summary information, extracted from the research literature, about the different types of physical function tests used with patients in CKD stage 5 have been summarised by Greenwood et al. 2014 and by Segura orti et al. 2021. For a more detailed description to aid practitioners in implementing the KDOQI guideline for assessment of physical function, recommendations, and encouragement for physical activity into practice, interested readers are referred to the review by Painter and Marcus (2013).[33] In addition to physical function tests, validated patient-reported outcome measures should be obtained to establish the improvement in health-related QOL (HRQOL), in particular self-reported physical activity status. The Dukes Activity Status Index (DASI) is a self-administered questionnaire that contains 12 questions relating to instrumental and life participatory ADLs, which the patient scores their perceived level of ability against.[34] In summary, physical function measurement outcomes can be used to:

- Establish the degree of functional impairment and identify the optimum timing for interventions.
- Evaluate the presence and severity of symptoms and adverse clinical outcomes such as muscle wasting, angina thresholds, etc.

- Determine safe and effective exercise rehabilitation training zones.
- Evaluate response to therapeutic interventions.

Intradialytic Cycling—A Pragmatic Approach to Encourage Uptake of Exercise and Physical Activity Promotion

A pragmatic approach to the prescription and delivery of intradialytic exercise training may be utilized as an integrated kidney-disease rehabilitation plan in the dialysis unit. The following pragmatic approach to exercise training for dialysis patients was generated by members of the British Renal Society Rehabilitation Network (BRS RN).[35] An understanding of the key components of exercise programming and prescription is integral to the delivery of a safe and effective program.

Patient Suitability for Starting an Exercise Program

The following exclusion criteria should be considered before any patient is accepted for an intradialytic exercise program:

- myocardial infarction within 3 months
- **unstable** angina
- acute infection
- acute orthopedic condition
- uncontrolled hypertension (> 180/100)
- uncontrolled arrhythmia
- other conditions raising concern over fitness for exercise should be discussed with the patient's consultant

On-the-day exclusion might also include:

- symptomatic hypotension
- low blood glucose
- cannulation/fistula problems
- excessive fluid overload (> 4 kg)

Staffing

Ideally, a specialist nephrologist would advocate cycling on dialysis when a patient first starts on dialysis with the intention of introducing exercise as an additional aspect of patient care, which, should it be followed on a regular basis, has the potential to translate into enhanced health and well-being benefits for the patients. Physician approval for physical activity has been cited as an important facilitator for patients engaging in exercise.[33–36] They are optimally placed to provide the medical assessment of suitability for the exercise program and ongoing medical support. This then means that a qualified member of staff, whether that is a physiotherapist, a nurse, or a dietician, would be able to lead patient management in this program. The aim is that intradialytic cycling becomes an available component of an HD session for suitable patients. Ideally, there should be an "Exercise champion" for each unit to promote the service and liaise with either the nephrologist or physiotherapists should any concerns arise.

Equipment

There are several designs of exercise cycles used in dialysis units: free-standing models, exercise cycles that attach to the dialysis chair/couch, and models that can be positioned for use on a hospital bed. Examples of this equipment can be found on the Bangor University website through the MOVE resources that have been created for intradialytic cycling (http://move.bangor.ac.uk/documents/Intradialytic-Cycling-Equipment.pdf).

The option chosen may be dependent upon the type of dialysis couch in operation in the dialysis unit or whether patients are dialyzed on hospital beds.

Pragmatic Exercise Prescription Approach

Patients should wear appropriate footwear and adopt a well-supported upper body and lower back body stature that does not overstress the shoulder and lower back muscles (depending on the mode and cycle ergometer) during leg cycling. The first 5 minutes of cycling should be a progressive warm-up (starting slow and increasing intensity), and the final 5 minutes should be the cool-down phase. Primarily reduce the intensity to 30% to 50% of the conditioning workload for 3 minutes and then to 20% to 0% for another 3 minutes. The duration and intensity of exercise prescription should be increased according to patient tolerance, using the following steps as a guideline.

1. The initial prescription should be based on the exercise assessment. If using an intradialytic cycle, then this can be used for the assessment. The exercise intensity should aim to be around 50%–60% of the power output that could be achieved at baseline assessments. If possible, the patient should achieve 20 minutes during the first dialysis session, with a rest in between. Otherwise, aim to do 10 minutes of cycling, either as five 2-minute or two 5-minute sessions (short rests in between).
2. Begin to increase the duration of exercise gradually. Aim for 30–40 minutes. The aim should be to increase the intensity of the exercise to 70%–80% of baseline power output achieved over the longer term.

The Rate of Perceived Exertion (RPE) scale,[34] or a similar outcome, can be used to monitor the patients' perceived effort level and ensure that the patient is exercising at a level that corresponds to moderate effort. If using the RPE scale, the patient should be asked to rate himself or herself during

the training time of the program, optimally aiming for their RPE between 13 and 15, "somewhat hard" to "hard." For each exercise session, the resistance, distance, time, and RPE from that session should be recorded, as well as any reasons for stopping or not partaking in the exercise training. This information can be used for progression, sharing achievements with patients, and assessing compliance with the program.

Goal Setting

It is important to ascertain a patient's motivation to increase their exercise levels and likeliness to adhere to the program.[37] To do this, behavioral change techniques such as motivational interviewing can help to resolve ambivalence for starting the program and encourage a patient to continue. Goal setting is another important aspect of any exercise program and can be an effective way of improving motivation, as well as the likelihood of achievement. The goals must be specific, measurable, achievable, realistic, and timed (SMART), for example, to be able to walk up one flight of 12 stairs, with no rests, within 3 months. Ideally, goals should be set at baseline and reassessed at consistent time points, whether that be three- or six-monthly, by an exercise professional. Practical resources for goal setting can be found at https://www.cardiosmart.org/~/media/Documents/Fact%20Sheets/en/abk5619.ashx.

Competence

Training, provided by a physiotherapist or an exercise physiologist, to all staff involved in the intradialytic cycling program is important. Staff should be deemed competent to:

- Assess the patient's ability to exercise, including validated outcome measures.
- Be able to identify when a patient is not suitable to exercise.
- Design an appropriate exercise program based on the exercise assessment.
- Progress the patient's exercise intensity to an individual level using RPE or an alternative scale.
- Use the equipment safely, adhering to manual handling policies.

Potential Barriers and Solutions to the Provision of Intradialytic Exercise Programs

In order to successfully implement an intradialytic cycling program and develop a sustainable longer-term exercise and physical activity plan, it is crucial to appreciate the global barriers to implementation and then consider localized barriers that may need to be problem solved within individual HD units. Preexisting exercise beliefs of patients and HD unit staff members can be a strong demotivating factor for exercise. Staff members caring for patients receiving HD therapy may consider patients as "too old"[38] and "too unwell" or "uninterested"[39] in undertaking exercise during dialysis. When surveying 100 patients receiving HD therapy, Delgado and Johansen[39] found the main patient barriers to exercise as fatigue on HD days (67%) and non-HD days (40%), shortness of breath (48%), and lack of motivation (42%). Often, these identified patient barriers can be problem solved through considering a holistic patient-centered approach utilizing motivational interviewing techniques to set patient-specific, meaningful, and achievable goals to assist with compliance in the initiation of exercise and the maintenance of longer-term exercise behavior. Some other possible non-patient-related reasons for the lack of provision of intradialytic exercise may include lack of exercise expertise, lack of knowledge and/or incentive among nephrologists, lack of facilities, a lack of financial incentives, funding for staff time and equipment, a poor understanding of the benefits of exercise therapy, and a fear of complications. A recent qualitative research study interviewing HD staff members revealed the low confidence of junior team members, who expressed the need for a specialist with nephrology and exercise expertise to support the prescription of intradialytic exercise.[40]

Common safety concerns from health care professions with implementation of intradialytic exercise have been identified as exercising the hypertensive or fluid overloaded individual undergoing maintenance HD, as well as the timing of the exercise session during dialysis session due to the perceived risk of hemodynamic instability. Wilund et al. (2019) addressed these concerns in a recent review, describing the evidence to support or refute these beliefs. In summary, these beliefs overall have led to a conservative approach to exercise prescription in this population.[41]

There are a number of potential strategies that could be utilized at a local level to tackle some of the potential barriers to implementation of an intradialytic exercise program. Involving members of the nephrology multidisciplinary team, such as kidney disease-specific physiotherapists or exercise physiologists, who are well equipped to provide specific and individualized exercise prescription while appreciating confounding comorbidities, can facilitate a change in the "exercise culture" of a dialysis unit. Visiting a dialysis unit with an active intradialytic exercise program may alleviate initial fears about implementing a program. There are also resources available, like the British Renal Society's Physical Activity network website (www.britishrenal.org/Physical-Activity).

The Way Forward—Translational Rehabilitation

The evidence for the benefits of physical activity for patients with CKD is accumulating, and encouragement to exercise and lead a physically active lifestyle is included in national CKD management guidelines.[42] The challenge is, quite clearly, how to translate the research findings into routine clinical practice. Strong evidence for the beneficial effects of exercise in nonresearch settings comes from the Dialysis Outcomes and Practice Patterns Study (DOPPS), published in 2010.[43] A cross-section of 20,920 DOPPS participants in 12 countries from 1996 to 2004 was reviewed. Regular exercise was associated with better HRQOL, better physical functioning, fewer limitations in physical functioning, better sleep quality, less intrusiveness of body pain or anorexia, a more positive affect, and fewer depressive symptoms. The offering of exercise in a unit was associated with 38% higher odds of patients exercising. Finally, overall mortality risk was lower in those units with more exercisers. Further research is currently underway in the UK, namely, a multicenter randomized controlled trial (RCT), The PrEscription of Intra-Dialytic Exercise to Improve Quality of Life in Patients with Chronic Kidney Disease (PEDAL) (ISRCTN83508514).[44] This research aims to review the effectiveness of intradialytic cycling on patient-centered outcomes in comparison to usual care. Another clinical trial within the UK currently underway is an RCT: Improving Cardiovascular Health in Patients with End-Stage Renal Disease Using a Structured Programme of Exercise: A Randomised Control Trial—"Cycle-HD."[45] This aims to test the hypothesis that an intradialytic program of exercise leads to a regression in left ventricular mass, an important nontraditional cardiovascular risk factor in kidney failure.

The following are suggestions for ways that might be adopted to facilitate the incorporation of exercise therapy into routine care.

- Education, support, advocacy
  This should be offered to nephrologists in post and in training and to nurses.
- Exercise promotion and provision should be offered as part of routine care in all nephrology units.
- Standards of care relating to exercise rehabilitation, endorsed by national and professional bodies, should be developed, with an agreed timescale for their implementation. The participation of representative patients' groups (National Kidney Federation in the UK) should be part of these activities.
- The documentation of functional capacity initially and serially after the start of dialysis should exist in all national registries. In addition, every unit undertaking exercise promotion and delivery should document its effects and associations as part of routine care.

Areas in which no clear conclusions can be drawn from the current research literature that need to be addressed are the effects of exercise on vascular function and incidence of cardiovascular events, dialysis efficiency, nutritional supplementation, BP, and systemic inflammation.

Thus, although the research evidence base needs enriching, the association between adequate levels of exercise, physical activity, and better outcomes in the dialysis population is sufficiently strong to state the following. It is now time, as has been stated by a number of authors of previous reviews, for nephrologists and their multidisciplinary team colleagues, for their professional bodies, and for government health departments to recognize the importance of this important health-enhancing behavior for people receiving kidney disease care. Exercise rehabilitation for CKD patients should be considered in dialysis units and offered to patients as an option in order to enhance confidence and efficacy in increasing physical activity.

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Physical, Psychosocial, and Vocational Rehabilitation of Patients Undergoing Long-Term Dialysis

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Whatever the cause of kidney failure, for most patients, the effects are the same. The insidious progression of symptoms parallels the slow worsening of blood chemistries as glomerular filtration declines. Many patients fail to recognize the change in their vigor and well-being and simply adjust to serial changes. This allows marked losses in exercise capacity and endurance to occur as deconditioning proceeds. Similar slowing of mental processes impairs relationships and communication. Dialysis removes most of the accumulated metabolites but does not restore lost abilities. Those require, at least, exercise and stimulation to recover. This chapter addresses the additional efforts needed to rehabilitate patients undergoing long-term dialysis and the reasonable expectations for improvement.

Background

Concern for rehabilitation has a long history in kidney failure. Advocates for Medicare benefits for dialysis and transplantation before the 1972 legislation made public assurances of the restored productivity of successfully treated patients, predicting that benefits provided would be returned in part by taxes paid by reemployed patients. Such enthusiasm was appropriate to the patients of that era of severely limited resources: each was carefully reviewed and accepted because of their ability to resume an active life with correction of uremia. Nephrologists reporting these results to encourage funding for dialysis and transplantation did not project what would ensue with open enrollment of all comers into kidney replacement therapy.

After implementation of the Medicare End-Stage Renal Disease (ESRD) Program in 1973, the dialysis population rapidly expanded—and just as rapidly ceased to be a uniform, motivated, youthful population with little comorbidity. As well, return to productive employment ceased to be the norm. Because the only definition of rehabilitation used was vocational rehabilitation, there was a widely perceived failure of the ESRD Program to fulfill its promise. Many in Congress and elsewhere felt betrayed. Nephrologists were embarrassed, and rehabilitation dropped from their vocabulary.

In place of rehabilitation, the focus turned to mortality and hospitalization (which also got worse with older, sicker patients)—and to the development of improved technology. By the time the U.S. Renal Data System (USRDS) was developed, using the Medicare database to shine a unique spotlight on the care of patients with kidney replacement therapy, the emphasis had changed from the large numbers of people who survived kidney failure with treatment to the number of dialysis patients who had short survival, poor health, or both.

Redefining Rehabilitation

The initial definition of rehabilitation addressed only the restoration of gainful employment, partly because of its potential economic consequences and partly because it was hard data easily used for assessment of outcome. It was widely remarked that in the absence of employment as the standard, no one knew how to define rehabilitation.

Despite those remarks, other medical communities recognized that there are also psychosocial rehabilitation and physical rehabilitation in addition to vocational rehabilitation. Efforts to improve and monitor outcomes in those areas were often used by general internists, physiatrists, social workers, exercise therapists, and others. Cardiac rehabilitation has become nearly universal after cardiac injury or surgery.

The nephrology community has many clinicians who always sought to understand the lifestyle and problems of their patients and to help them cope with and improve their lives, but this was an individual effort—with no systematic

structure, no standards or guidelines, and no national or regional recognition. The results were reported as anecdotes of fulfilling experiences for professionals, as well as successes for patients—but not as clinical trials in medical journals. The impact of these experiences was quite limited.

In 1993, with support from Amgen, the Life Options program was started, and the Life Options Rehabilitation Advisory Council (LORAC), composed of experts in dialysis care and psychosocial research, was established to lead it. The Council's members set out to define an orderly structure for rehabilitation efforts that would include physical, psychosocial, and vocational rehabilitation arenas and that would provide guidance to clinicians and facilities undertaking it. This program is not the only such effort, but the organization of ideas and the subsequently reported successful programs make it an easy model for application to most dialysis treatment sites, as well as to other chronic disease settings.

Life Options begins with the "five Es" of rehabilitation for kidney disease (Table 61.1). The approach starts with *encouragement*, believing that the person can do better and that everyone involved will be gratified by the accomplishment, gently (or forcefully, if necessary) stimulating the patient to make an effort to be healthier. The *evaluation* that individualizes the approach can be included in the clinical planning for each patient, required by regulations and routinely documented. This includes education, work history, former and recent activity levels, physical capacity, social support, interests and hobbies, and hopes for the future. Patients need to know that this is happening, need to be informed, and need to make some choices in their plan. Interval reevaluation is important both to adjust the program and provide everyone involved with a means of measuring what has been accomplished. Recognition of even small steps forward can mean a great deal. Setting a goal individualized to each patient's needs and capacities in clear and measurable terms and noting milestones as each is reached will ensure that all participants are rewarded.

TABLE 61.1 Life Options' Definition of Renal Rehabilitation

- *Encouragement:* Surround the patient with a positive attitude.
- *Education:* Learn about kidney disease and dialysis, and about opportunities and interests.
- *Exercise:* Essential to recover and maintain physical capacity; improves cardiovascular health.
- *Employment:* Maintain or return quickly when possible; understand barriers and benefits.
- *Evaluation:* Repeated assessment of status and changes; important for factual reinforcement (along with regular assessment of functional status and health-related quality of life).

Education begins with each patient learning about kidney failure and the dialysis regimen; follows with health improvement goals, functional expectations, and exercise methods; and continues through specific learning to enable progress toward specific goals. Self-management of this regimen and direction is encouraged. Subsequently, this may include outside agencies or individuals. Some patients may not progress past the simplest grasp of their situation, but every patient needs enough knowledge to minimize fear of their disease and its treatment and lessen dependence on staff and family. The opportunity to learn about subjects of interest may activate patients.

Almost every patient needs *exercise* because most undergo significant physical deconditioning with loss of capacity and endurance as the disease progresses. The "spiral of deconditioning" is quickly recognized by most patients and clinicians as accurate. Loss of vigor is so gradual that the patient often does not recognize it. Exercises to reverse this decline need to be light but regular, composed of repetitions capable of being counted so that there will be a tangible reward through achieving higher counts, which reveals improved physical capacity. Most patients can train themselves to physical capacity near premorbid levels. Work using this approach has shown that patients' peak oxygen uptake improves after successful physical training, an objective measure of improved functioning.

Stationary bicycles, treadmills, and other exercise devices are effective and have been installed in some dialysis facilities. Some are used before dialysis; others have been adapted for use during the usually boring time spent on dialysis. Exercises during dialysis are usually well tolerated without disrupting the procedure.

Everyday objects may also be used for exercise. A chair can be used for bracing during movement or seated leg exercises. Canned goods can be used as dumbbells. Large rubber bands (Therabands) are used as a resistance to pull against. A sandbag can serve as a flexible weight that can be held on a foot to exercise a leg or in a hand to exercise a shoulder. Walking is always a good exercise for those who can. Walking indoors works when weather or neighborhoods discourage going outside. A few steps up and down the stairs are easy to repeat and count, with numbers increasing as exercise builds endurance.

Most of these simple actions build strength for activities of daily living. Periodic reassessment provides the patient with a satisfying reinforcement of accomplishment. It is important to promote expectations of well-being sufficient for continued productive living and independence and then to demonstrate that ability. Counting repetitions is simple. When more quantitative results are sought, the standard 6-minute walk, stand-sit-stand test, or measured grip strength may be used. Loss of confidence may be as limiting as the loss of physical strength. Repeated reinforcement of progress through objective measurements can rebuild confidence.

The goal of *employment* is not realistic for most dialysis patients. Published reports confirm that those already employed can often retain employment or return to it promptly with less difficulty than trying to place an individual in a new job. Success is also related to education level. Vocational rehabilitation agencies and private employment companies can provide evaluations, arrange some types of training, and make potential employment contacts. The enthusiasm for such services must often come from the patient or the dialysis staff assisting the patient. Vocational rehabilitation offices are more accustomed to amputees, persons impaired in vision or hearing, or others with more obvious physical deficiencies, and some workers there may be ill at ease with a dialysis patient's problems. The pool of those who want to work or who can realistically become employable may be small, but for those few, even a part-time job can be a great advantage. Working produces income and provides tangible evidence of recognition and personal worth, sets a framework for living through a regular schedule, and helps maintain physical capacity.

A survey of dialysis patients 18 to 55 years old found that more than 30% believed themselves able to work, but fewer than 20% were able to be employed. The clinical team must realize the potential for employment and support the effort if patients are to succeed. In addition, a number of patients are known to work part time or "off the books" to avoid loss of disability benefits, which compete well with what many can earn.

Other life-enhancing activities are more widely available than returning to employment. The mean age of dialysis patients is over 60 years, and many are beyond employability. However, some of them can discover useful and rewarding roles as volunteers or as members of other community activities that engage them in life outside their home, distracting them from focusing on health problems. These activities meet a broad definition of rehabilitation. Not just the elderly but also the majority of dialysis patients can improve their physical, social, and intellectual functioning through education (in living with dialysis, in crafts, in history, arts, or specific interests) and through exercise during, before, or after dialysis in an entertaining way.

With encouragement, most patients can find ways to incorporate simple physical conditioning into daily activities. Encouragement from many sources (family, staff, volunteers, other patients, and so on) underlies the patient's acceptance and promotion of their own health. The clinical team's evaluation of results and feedback to the patient and family of the findings can reinforce the rewards of self-improvement efforts on a number of levels. All of these can aid in establishing groups for shared activity, increasing social interaction, and avoiding isolation.

Every practicing nephrologist can relate stories of individual patients who are not responsive to any effort at motivation, whose behavior and lifestyle frustrate everyone. Positive support for good habits and visible recognition of self-improvement achieved by other patients help to prevent bad habits from becoming contagious. These failures do not merit emphasis but sometimes can be seen as an object lesson for other patients who would avoid their fate. Expecting effective rehabilitation will not always succeed, but expecting failure fulfills itself easily. For clinicians, the success of some patients can make tolerable the frustration caused by other individuals.

Prerequisites to Effective Rehabilitation

Comorbid Conditions and High-Risk Lifestyles

Control of comorbid conditions such as hypertension and heart failure is a routine consideration for the dialysis population because these conditions are frequent in kidney failure. Rehabilitation requires each individual to reach their optimal health and to realize adequate stability for the confidence to try to expand capabilities. Medications are usually effective for these conditions, but effective sodium and volume restriction and regular physical activity, such as some of the exercises previously mentioned, promote cardiovascular health.

Systematic monitoring of cardiac function through periodic echocardiograms and other testing can guide clinical management and recognize new problems in established cardiac disease. For patients with diabetes, better control of glucose and blood pressure helps preserve vision and cardiovascular function even after the onset of kidney failure. For those with demonstrated vascular disease, control of serum lipids is important to preserve circulatory function. This often requires cholesterol-lowering medication as well as lifestyle modification. All of these factors merit attention as part of the health plan that underlies rehabilitative efforts.

Diet and activity are cultural practices. Changing them requires patients to learn the reason for changes. Repetitive monitoring and reinforcement aid motivation. People can be encouraged to change their habits by compensating enrichment of relationships, surroundings, or other pleasures that reward adherence. This is often beyond the reach of dialysis clinicians, but there are some conditions we can change (e.g., schedule and companions during treatment). Other conditions only need to be pointed out emphatically (e.g., weight loss, improved exercise capacity, and better laboratory values).

Depression is common in people undergoing long-term dialysis. If exercise can restore vigor, spirits often rise as well. Clinicians need to be sensitive to clues to mood change and depression because these can affect adherence, nutrition, activity, and survival. Patients with physical disease and depression often respond well to antidepressant medication or cognitive behavioral therapy.

Family Participation

Families may be protective of patients to the point of promoting dependence or preventing activities that can improve their functioning. The family needs to be included in

learning and reinforcement of desirable behavior. Families need reassurance that denying a wish that adds to disease is the right thing to do, even if it causes friction. Patients behaviorally regress as they become limited by disease, acting more childlike in many ways. Families have to deal with that behavior more than clinicians, and their easiest coping mechanism may be to yield to requests that break the regimen and promote comorbidity. Older patients, in particular, may retreat and withdraw, making it difficult to engage them in the social and physical activity necessary to promote health. Family members need to make efforts to break this pattern, but many find it difficult to exercise authority over parents. Support and education from the clinical team can help them understand and act appropriately.

Implementing Rehabilitation

Effective rehabilitation efforts require that everyone endorse the concept and commit to the program. Administration must commit resources of staff time and space to enable these activities. They have to value the goal, or they will not invest to reach it. The medical director and other nephrologists must accept the idea and promote it because attitudes and values often come from the doctors.

Nurses and clinical technicians must consistently reinforce the goal of rehabilitation and encourage the activities leading toward it in their repeated contact with patients. Consistent positive attitudes move the program forward and improve the atmosphere in the facility at the same time. Social workers can coordinate outside agencies and contacts to assist patients, and their contacts with patients can be most effective in building a positive attitude in them. Because nutrition is fundamental to gaining strength and feeling better, dietitians have opportunities to show patients how learning and following a regimen make them healthier.

Some individuals on the staff, often a social worker or dietitian but also frequently a nurse, must be named responsible for coordinating the rehabilitation program and for monitoring outcomes accomplished. The coordinator must be supported by all staff, not abandoned in the position because patients often need help from multiple sources to succeed.

The coordinator may lead groups of patients in exercise activities or designate another person to do so if exercise in the facility is undertaken. Any staff member can teach simple exercises for patients to do independently, at home, or in dialysis. All staff can help with education and must consistently encourage patients to make the effort—and then cheer the results. Rehabilitation is a team effort. These steps can be a byproduct of existing practices and contacts. The theory is simple: A group of people consistently believing that trying will accomplish something good for patients can convince patients to make an effort. Then everyone can enjoy the results, and the facility is a more pleasant place.

Evaluation of Outcomes

Employment, as noted in the historical review, is readily documented. Physical improvement is less so. Self-reports from patients are valuable, but it may be useful to observe and count repetitions of simple exercises or use a standard measurement, such as stand-sit-stand (as many times as possible in 30 seconds), the 6-minute walk (probably too time consuming to do for a group), or measured grip strength. Attitudes and increased knowledge are subjective but definite, and they merit notation.

An overall assessment through self-report of a standard health or functional status questionnaire or health-related quality of life form is now a regular practice in dialysis, and the results correlate well with survival and hospitalization and predict behaviors that may affect the course of dialysis. These self-reported data demonstrate good correlations with more conventional clinical outcomes and offer interval assessment of health status that can guide clinicians' efforts to improve functioning and well-being.

Applying these instruments and using the scores obtained to assess progress toward rehabilitation have been recommended as the single most useful indicator of an effective approach to rehabilitation in a dialysis facility. There are accepted, recognized instruments of considerable experience that may be valuable to a facility in assessing the patient's perception of progress. Such reports, used semiannually, give a numerical score that can be followed as an integrated evaluation by the patient of the outcome of care. These results can point out aspects of care that need attention, just as laboratory test results and physical findings can guide the dialysis prescription.

As patients undergoing long-term dialysis become “older and sicker,” it is easy to give up hope of improvement or accomplishment for many. However, when the five Es are applied as part of dialysis care, every patient has an opportunity to improve themselves and become rehabilitated in terms specific to them. The results reported in a number of facilities confirm that as attitudes and communication improve demonstrably, improved functioning occurs, and the staff share in the rewards they have helped patients achieve. When rehabilitation is defined as helping each patient reach their highest level of functioning and satisfaction, the goal is reasonable, individually achievable, and beneficial.

Conclusions

The amount of time that dialysis patients and staff spend together invariably exerts influence. It can be an opportunity to enrich one another's lives in ways that encourage and reward healthy behavior, leading to rehabilitation as defined here. All such endeavors take time, and current constrained finances in dialysis care make this difficult because time is in short supply. Using milestones and giving guidance toward rehabilitation have to be incorporated into the obligatory contacts of treatment, or there will not be time to do

these things. Health promotion and rehabilitation have to be a central part of therapy, not an additional or peripheral aspect of care that receives attention only after other steps are complete. When physical, social, and sometimes vocational rehabilitation are the goals of treatment, dialysis can become a holistic therapy.

Expecting people on dialysis to return to active lifestyles, whether employed or not, is not always successful. However, expecting passivity, depression, and progressive physical deterioration will usually lead to just those outcomes. The social environment in a dialysis facility is conditioned by the expectations of clinicians and their response to good results. Rehabilitation will not occur passively. The matrix of adequate use of effective technology, good nutrition, appropriate medication, and medical monitoring is fundamental to dialysis care and essential for effective rehabilitation. A conscious, organized plan to help each patient improve according to individual capability is the next step toward improved health. Working partnerships between patients and clinicians can succeed in promoting greater health, confidence, and positive attitudes. These attributes are themselves one level of rehabilitation for many patients.

Rehabilitation and the promotion of optimal health accompanying it is best seen as the central goal of treatment—not as an addition to treatment. It is effectively addressed as part of routine care as much as dialysis, medication, and diet when incorporated into the framework of care in this fashion. Once clinicians are comfortable with their knowledge of rehabilitation, the contact with patients includes observations, recommendations, instructions, and assessments of their health status without a great increase in contact time.

Programmed exercise before, during, or after dialysis requires some oversight, which will consume time for a staff member able to supervise exercise. Surveys for health and functional status and quality of life measurement are largely self-administered but scoring and handling require some staff effort. Analyzing and using these results in focusing attention and improving care take thought and practice. Helping patients to make themselves well is achievable. The rewards of improved productive living for patients, improved satisfaction for staff, and stabilizing the patient population (which preserves facility income) make renal rehabilitation a positive experience for all concerned.

Recommended Reading

Capelli J. Implementing organizational systems to measure outcome-related processes of end-stage renal disease care. *Am J Kidney Dis.* 1994;24:346–354.

Practical and detailed report of developing systematic assessment of operations and outcomes, including aspects of rehabilitation and associated characteristics. Provides guidance in systematic analysis and use of operational data to improve care.

DeOreo P. Patient assessed functional health status (FHS) predicts survival in hemodialysis (HD) patients as well as Kt/V and nPCR do. *J Am Soc Nephrol.* 1996;7(9):1444.

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Important article demonstrating the importance of functional status and quality of life assessment. Based on data from a multicenter program with good data collection and analysis.

Gutman R, Stead W, Robinson R. Physical activity and employment status of patients on maintenance dialysis. *N Engl J Med.* 1981;304:309–313.

Broad survey of poor employment and physical capacity results of maintenance dialysis. The first attempt at objectively defining results for dialysis patients under Medicare.

Kurtin PS, Davies AR, Meyer KB, et al. Patient-based health status measures in outpatient dialysis: early experiences in developing an outcomes assessment program. *Med Care.* 1992;30(5):MS136–MS149.

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van Vilsteren MC, de Greef MH, Huisman RM. The effects of a low-to-moderate intensity pre-conditioning exercise programme linked with exercise counselling for sedentary haemodialysis patients in the Netherlands: results of a randomized clinical trial.

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Preventive Care in End-Stage Renal Disease

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Preventive care of dialysis patients encompasses general medical care issues as well as dialysis-specific issues that are detailed in preceding chapters. In this chapter, aspects of general medical preventive care are discussed as they apply to maintenance dialysis patients. The transplant status of a patient will affect some of these issues. For example, recommendations for cancer screening and immunizations will in part depend on the patient's transplant status, and when relevant, this will be noted. Specific patient recommendations for preventive care are based on the individual patient's prognosis and risk factors. The suggestions for dialysis patient preventive care that follow need to be individualized for specific patients by their nephrologists and dialysis care providers. Preventive care can be categorized into immunizations, infection prevention, screening, health care counseling, advance care planning (ACP), supportive care, and disease monitoring. Each of these is discussed in this chapter.

Immunizations

Table 62.1 lists the Centers for Disease Control and Prevention (CDC) recommendations for immunizations in dialysis patients based on age and transplant status. Although dialysis patients generally have a lower immunologic response and develop lower and less sustained antibody titers to immunizations, the CDC recommends vaccinating all dialysis patients. Despite less robust antibody responses, dialysis patients may be protected from infection, and vaccinating dialysis patients may reduce the risk for virus transmission in dialysis units. Altering immunization schedules and vaccine doses may, in some cases, improve the antibody response in dialysis patients. Dual vaccination (e.g., simultaneous tetanus and hepatitis B) has also been observed to improve antibody responses in dialysis patients. Live vaccines (varicella zoster, intranasal influenza, measles, mumps, rubella, yellow fever, bacillus Calmette-Guérin, and oral *Salmonella typhi*) should not be administered to transplanted and immunosuppressed patients and thus should be given based on clinical circumstances.

Hepatitis B Vaccine

Table 62.1 summarizes the recommendations for vaccination. Because hepatitis B is transmitted via inoculation through exchange of blood products or body fluids and was responsible for infection outbreaks in dialysis units in the 1980s, hepatitis B vaccination is recommended for all dialysis patients, and monitoring for antibody protection is required. Only 34% to 88% of dialysis patients will develop immunity through vaccination, which is therefore suggested early in chronic kidney disease (CKD) to take advantage of a better-preserved immune response with less severe kidney disease. Vaccine manipulations (higher dose, extra doses, coadministration of immune modulators, or other vaccines) may improve the antibody response. Patients who do not respond to an initial vaccination series should have the series repeated once. Patients who lose antibody titers after an initial response to the vaccine should receive a booster dose. The precise timing of monitoring antibody titers is unclear.

Influenza and H1N1 Vaccine

Similar to the case with other vaccines, dialysis patients develop variable responses to influenza; 36% to 90% develop protective antibodies. Response to the H1N1 vaccine is similar, with 33% to 64% of dialysis patients developing antibodies. Older studies suggested that hospitalization and secondary pneumonia were more common among dialysis patients with influenza, leading to the recommendation that all dialysis patients receive yearly influenza vaccines. A more recent study suggested only a small benefit of influenza vaccination in dialysis patients but raised the issue of addressing vaccination strategies to maximize dialysis patient vaccine response (e.g., high-dose trivalent vaccine may be preferable in dialysis patients as it is in older adults; see Table 62.1). More recent studies comparing the high-dose influenza vaccine with standard-dose vaccine in dialysis patients found no significant difference in morbidity or mortality with the high-dose vaccine.

TABLE 62.1 Recommended Adult Immunizations for Dialysis Patients

Vaccine	Dosing and Information
Hepatitis B	40 μg Recombivax HD on three-dose schedule or 40 μg Engerix-B on four-dose schedule
Hepatitis A	Only if another risk factor is present
Human papillomavirus	Female—two or three doses through age 26 years depending on age at initial dose
	Male—two or three doses through age 26 years depending on age at initial dose
Influenza	Age ≥19 years trivalent vaccine yearly
Measles, mumps, rubella	One or two doses if no immunity
Meningococcal	Only if another risk factor is present
Pneumococcal	Age ≥19 years, one dose PCV13 followed by one dose PPSV23 at least 8 weeks later; repeat PPSV23 in 5 years
Tetanus, diphtheria pertussis	One-time dose of Tdap (tetanus, diphtheria, and pertussis); then boost with Td (tetanus and diphtheria) every 10 years
Varicella zoster	Age ≥50 years two doses recombinant vaccine

PCV13, Pneumococcal conjugate vaccine; *PPSV23*, pneumococcal polysaccharide vaccine.
Based on Centers for Disease Control and Prevention. Recommended Adult Immunization Schedule. http://www.cdc.gov/vaccines/schedules/downloads/adult/mmwr-adult-schedule.pdf.

Tetanus, Pneumococcal, Human Papillomavirus, and Varicella Zoster Vaccines

There are few studies of antibody response to these vaccines in dialysis patients. Similar to other vaccines, the antibody response tends to be suboptimal and short-lived. The CDC continues to recommend routine vaccination of dialysis patients with these vaccines (see Table 62.1). If the patient was younger than 65 years of age upon initial pneumococcal vaccination, an additional dose should be given 5 years later. A tetanus, diphtheria, acellular pertussis vaccine became available in the United States in 2005 for those 11 to 64 years of age. A single booster vaccine dose is suggested for adults and is given 2 years or less after the initial vaccine in high-risk individuals. There is little information on the safety and efficacy of varicella zoster and human papillomavirus (HPV) vaccines in dialysis patients. Small studies suggest that girls with CKD developed antibodies to HPV vaccine, and thus, those less than 26 years of age should be vaccinated. The Shingrix vaccine is a recombinant vaccine (not a live vaccine like the older Zozstavax vaccine) and should be given to all dialysis patients over 50 years of age (see Table 62.1).

Infection Prevention

Probably because of their impaired immune response, including reduced B- and T-cell responses and phagocytosis, dialysis patients have a higher incidence of and are at higher risk of poor outcomes and complications with bacterial infections. Efforts to reduce dialysis access–associated infections may include the local application of antibiotic creams to access exit sites and intranasal application of antistaphylococcal creams in nasal carriers. Antimicrobial prophylaxis should also be considered a preventive strategy.

Diabetic Foot Care

A routine diabetic foot care program, including nursing assessment and patient education, may be associated with better footwear adequacy and a reduction in neuropathy, ultimately leading to fewer foot ulcers and wounds.

Dental Care

Periodontal disease, premature tooth loss, and xerostomia are more common among dialysis patients and can lead to systemic inflammation and morbidity. Some have implicated periodontal disease as an inflammatory factor contributing to cardiovascular disease in dialysis patients. Gingivitis and periodontitis are manifestations of poor dental health and are more common in dialysis patients. The cause of periodontal disease in dialysis patients is unclear, but impaired humoral responses and possibly bacterial colonization in response to repeated gingival bleeding from heparinization during dialysis have been postulated. Routine dental care (brushing, flossing, use of mouthwashes, and preventive care by dentists and hygienists) is also less common among dialysis patients. In addition, renal osteodystrophy can involve the mandible and maxilla, resulting in tooth mobility, malocclusion, enamel hypoplasia, metastatic soft tissue calcifications, and demineralization. Educating patients about the importance of routine preventive dental care may help to avoid subsequent issues and infections.

Endocarditis Prophylaxis

There are no data on the usefulness of antibiotic prophylaxis to prevent endocarditis in dialysis patients. However, for patients with known valvular abnormalities, prosthetic heart valves, congenital heart abnormalities, a history of endocarditis, or a heart transplant, antibiotic prophylaxis before dental or periodontal procedures is recommended. A single oral dose of amoxicillin (2 g) or clindamycin (600 mg) in those allergic to penicillin 1 hour before the procedure is recommended. Because of the high risk of endocarditis in the setting of a central venous catheter, dialysis patients with tunneled catheters should probably be considered for

antibiotic prophylaxis despite the lack of such recommendations by the American Heart Association (AHA). The generalized immune-suppressed state of kidney failure prompts some to argue for antibiotic prophylaxis for all dialysis patients undergoing invasive procedures and dental treatments. There are reports of peritonitis occurring after colonoscopy with biopsy in peritoneal dialysis (PD) patients. For this reason, many nephrologists suggest antibiotic prophylaxis according to the AHA endocarditis prevention guidelines in PD patients undergoing colonoscopies. All PD patients should undergo such procedures with a dry peritoneum to reduce the risk of bacterial seeding of the peritoneal cavity filled with dextrose-rich dialysate.

Tuberculosis Screening

Tuberculosis (TB) is more common in patients with kidney failure, ranging from 6 to 25 times higher than in the general population. Dialysis patients also have a higher risk of developing clinical TB after exposure. Thus, it is important to detect latent TB infection and offer treatment. The tuberculin skin test is based on a delayed hypersensitivity response to a purified protein derivative (PPD) of *Mycobacterium tuberculosis* but has limited sensitivity in dialysis patients. T-cell interferon-γ release assays are now available as screening tests for *M. tuberculosis* infection and seem to be more sensitive screening tests for latent TB infection in patients with kidney failure. Because of the possible spread of TB in a dialysis unit, consideration should be given to screening patients with one of the interferon-γ release assays (QuantiFERON-TB Gold In-Tube or T-SPOT.TB).

Screening

Several screening protocols are recommended in the general population, many of which can be reviewed online at the American Preventive Task Force's website (http://www.uspreventiveservicestaskforce.org). Some of the recommendations for screening for disease in the general population may be applicable to dialysis patients, but many will not be, in large part because dialysis patients have a lower expected survival, making development of the disease for which screening is suggested unlikely. When considering screening in general, therefore, it is important to consider not only the risk of that disease in the population being screened but also the likelihood that the patient to be screened will live long enough to benefit from screening. For populations such as those on dialysis, a poor prognosis will limit the cost-effectiveness of screening. In addition, one must understand the positive and negative predictive values of the tests chosen to use for screening. Some diseases to be considered for screening in dialysis patients include cancer, falls and frailty, abdominal aortic aneurysms (AAAs), alcohol abuse, cognitive impairment, depression, and hearing and vision loss.

Cancer Screening

Table 62.2 shows recommended cost-effective cancer screening in dialysis patients. The suggested screening varies from the American Cancer Society recommendations for cancer screening in the general population because the poor overall survival of dialysis patients limits the cost-effectiveness of some cancer screening. Some cancers, notably bladder and ureteral; renal cell (in the setting of acquired cystic disease); HPV-associated cancers such as cervical, uterine, and tongue; and hepatitis-associated liver cancer, are more common in dialysis patients, with standardized incidence ratios of 1.5 to 24.1 (Table 62.3). Generally, breast, lung, and colon cancers are not more common among dialysis patients. Stool hemoccult testing in dialysis patients is more likely to be positive, probably because of multiple reasons for gastrointestinal blood loss in dialysis patients. Thus, colonoscopies may be more common in this population. Hypothetical analyses to screen for cervical, breast, colon, and prostate cancer in dialysis patients have shown less than 5 days of life saved with screening. Dialysis patients who are not transplant candidates, those 50 to 70 years of age, and are white are least likely to benefit from cancer screening. Cancer screening among dialysis patients should be individualized and based on the patient's expected survival, risk for cancer to be screened, and kidney transplant status. Most transplant programs incorporate cancer screening into their transplant evaluation process.

Falls and Frailty

Falls

Falls occur more commonly among dialysis patients than in the general population, reportedly at a rate of 1.6 falls per dialysis patient-year versus 0.6 to 0.8 falls per patient-year in the geriatric population. Hip fracture is a common result of a fall and is four times more frequent among dialysis patients. Hip fractures are associated with higher mortality; thus, preventing falls in dialysis patients could theoretically reduce mortality and morbidity. Risk factors for falls in dialysis patients include older age, comorbid conditions, a history of falls, peripheral neuropathy, anemia, gait impairment, frailty, cognitive dysfunction, and mean systolic blood pressure. Dialysis-associated hypotension and fatigue may also contribute to falls, which are among the most common adverse events in hemodialysis (HD) units. Medications may increase the risk of falls, especially opioids, muscle relaxants, vasodilators, anticholinergics, benzodiazepines, and tricyclic antidepressants. Screening for fall propensity by routinely asking dialysis patients about falls (previous fall is a risk factor for future falls), fostering exercise programs to increase muscle strength, and minimizing polypharmacy may help to reduce the likelihood of falls. Formal testing for fall risk and investigation of the home for environmental fall risk factors may prove useful in individual cases. The American Preventive Task Force assigns level B evidence (should offer or provide) to screen for fall risk

TABLE 62.2 Suggested Cancer Screening in End-Stage Renal Disease Patients: Individualized, Considering Expected Survival, Risk Factors, and Transplant Status

Cancer*	Recommended Screening
Breast	40–44 years—mammography individualized based on patient wishes, risk factors, transplant status
	45–54 years—biennial mammography considering risk factors and estimated survival (estimated survival >10 years, in good health)
Colorectal	Beginning age 45 years: yearly fecal occult blood test (FOBT) or fecal immunochemical test (FIT) for those on transplant lists and flexible sigmoidoscopy, colonoscopy, double-contrast barium enema, or virtual colonoscopy per transplant evaluation protocols (usually every 5 or 10 years depending on risk factors)
	Positive FIT or FOBT result requires additional evaluation
Cervical	Begin screening at age 21 years;
	21–29 years: Pap smear every 3 years, no HPV unless Pap abnormal
	30–65 years: Pap + HPV every 5 years or Pap alone every 3 years
	>65 years: if normal for 10 years, no further testing
	Consider HPV DNA and HPV vaccine in transplant candidates
Prostate	Age 50 years, annual PSA and DRE for men on transplant list per transplant center protocol
	Age 45 years if African American or have father or brother with prostate cancer before the age of 65 years
Renal cell	Routine screening not recommended. May consider ultrasonographic or CT in patients on dialysis >3 years and on transplant list, especially if acquired cystic disease, analgesic nephropathy, family history, smoking history
Lung	Age 55–74 years with at least 30 pack-years smoking history and still smoking or quit within 15 years, consider annual low-dose CT based on expected survival and transplant status

* For all of these cancers, consider screening in high-risk patients with long expected survival times.
CT, Computed tomography; *DRE*, digital rectal examination; *HPV*, human papillomavirus; *PSA*, prostate-specific antigen.
Data from Holley JL, Screening, diagnosis, and treatment of cancer in long-term dialysis patients. *Clin J Am Soc Nephrol.* 2007;2:604-610; Holley JL. General medical care of the dialysis patient: core curriculum 2013. *Am J Kidney Dis.* 2013;61:171-183; Choudhury D, Luna-Salazar C. Preventive health care in chronic kidney disease and end-stage renal disease. *Nat Clin Pract Nephrol.* 2008;4(4):194-206; Butler AM, Olshan AF, Kshirsagar AV, et al. Cancer incidence among US Medicare ESRD patients receiving hemodialysis 1996–2009. *Am J Kidney Dis.* 2015;65(5):763-772; Wong G, Holley JL. Incidence of cancer and screening recommendations. In: Finkel KW, Perazella MA, Cohen EP, eds. *Onco-Nephrology*. St. Louis: Elsevier; 2020: 307-313; Yasin S, Holley JL. When ESKD complicates cancer screening and cancer treatment. *Semin Dial*. 2020;33(3):236-244; and American Cancer Society. American Cancer Society Guidelines for the Early Detection of Cancer. http://www.cancer.org/healthy/findcancerearly/cancerscreeningguidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer.

in those older than 65 years in the general population and recommends exercise or physical therapy in an attempt to prevent falls. Multifactorial interventions to prevent falls are assigned a level C recommendation, and vitamin D replacement is no longer recommended as a tool in fall prevention (level D evidence—recommends against).

Osteoporosis and Bone Mineral Density

The primary risk of falls is hip fracture. The benefits of bone densitometry screening for osteoporosis in the dialysis population are unclear. Although abnormalities of bone minerals are more common in patients with kidney failure, the complex nature of the abnormalities makes bone densitometry results difficult to interpret. Moreover, common treatments for osteoporosis, such as bisphosphonates, are not recommended in dialysis patients.

Frailty

In the geriatric population, the frailty phenotype is associated with disability, hospitalization, and mortality. Frailty is recognized as a clinically useful marker for complex cumulative stresses on a biologic model that leads to functional decline with attendant morbidity and mortality. The phenotypic definition of frailty includes three or more of the following: weight loss (10 pounds or more unintentionally in the past year), weakness (characterized by decreased handgrip), poor endurance and energy, slowness (walking speed >6–7 seconds for 15 ft), and low physical activity (19). Frailty is associated with hospitalization and death in dialysis patients and was seen in 67% of dialysis patients in the Dialysis Morbidity and Mortality Wave 2 Study. There are many screening tests for frailty, and these have been studied in the elderly CKD population, but a complete geriatric assessment remains the gold standard for identifying frailty. The components of a geriatric assessment include the domains of activities of daily living, sensory deficits, mobility including falls, mood and cognition, nutrition, comorbidity, polypharmacy, and social support. Identifying frailty among dialysis patients could potentially lead to interventions designed to forestall functional decline and its consequences.

TABLE 62.3 Cancer Incidence in End-Stage Renal Disease: Literature Summary

Cancer	SIR	Risk Factors in Kidney Failure
Renal cell	3.6–24.1	Acquired cystic disease
Bladder and ureter	1.5–16.4	Analgesic abuse, Balkan nephropathy
		Asian ethnicity, oral cyclophosphamide
Tongue	1.2–1.9	Human papillomavirus
Cervical and uterine	2.7–4.3	Human papillomavirus
Liver	1.4–4.5	Hepatitis B and C
Thyroid and other endocrine organs	2.2–2.3	
Breast (women)	0.8–1.42	
Lung or bronchus	0.5–1.28	
Colon or rectum	1.0–1.27	Human papillomavirus (rectal cancer)
Pancreas	1.08	
Prostate	0.5–1.08	

SIR, Standardized incidence ratio.
Data from Holley JL. Screening, diagnosis, and treatment of cancer in long-term dialysis patients. *Clin J Am Soc Nephrol.* 2007;2:604-610; Holley JL. General medical care of the dialysis patient: core curriculum 2013. *Am J Kidney Dis.* 2013;61:171-183; Choudhury D, Luna-Salazar C. Preventive health care in chronic kidney disease and end-stage renal disease. *Nat Clin Pract Nephrol.* 2008;4(4):194-206; Butler AM, Olshan AF, Kshirsagar AV, et al. Cancer incidence among US Medicare ESRD patients receiving hemodialysis 1996–2009. *Am J Kidney Dis.* 2015;65(5):763-772; Wong G, Holley JL. Incidence of cancer and screening recommendations. In: Finkel KW, Perazella MA, Cohen EP, eds. *Onco-Nephrology*. St. Louis: Elsevier; 2020: 307-313; and Yasin S, Holley JL. When ESKD complicates cancer screening and cancer treatment. *Semin Dial*. 2020;33(3):236-244. .

Abdominal Aortic Aneurysm

Depending on patient age, gender, and tobacco use, the American Preventive Task Force recommends screening for AAA. The best evidence (level B—should offer or provide) for AAA screening is in men 65 to 75 years of age who have ever smoked. Level C evidence (selectively offer screening) is reported in men 65 to 75 years of age who have never smoked. Women who have never smoked should not be screened, and there is insufficient evidence to recommend screening for AAA in women who have smoked. There are no comparable data in dialysis patients. Thus, similar to cancer screening in dialysis patients, it seems prudent to screen only dialysis patients with long expected survival and high risk for AAA.

Alcohol Abuse

There is little information about alcohol abuse in the dialysis population. One study in an urban HD group found that 27.6% of patients scored in the alcoholism range on the MAST (Michigan Alcoholism Screening Test), with the estimate in the general population ranging from 5% to 10%. Alcohol dependence at the time of diagnosis of kidney failure is associated with lower survival in those undergoing kidney transplantation. Additional study of alcohol abuse in dialysis patients is needed, including validation of commonly used screening tests. The American Preventive Task Force recommends the AUDIT-C (Abbreviated Alcohol Use Disorders Identification Test–Consumption: three questions asking about frequency of use, typical amount drunk, and occasions of heavy use) and the SASQ (Single Alcohol Screening Question: "How many times in the last year have you had 5 [for men] or 4 [for women and those >65 years of age] drinks in a day?") as screens for unhealthy alcohol use. If screening is positive, additional information should be obtained via AUDIT (Alcohol Use Disorders Identification Test, 10 questions) or other tools.

Cognitive Impairment

The American Preventive Task Force does not recommend screening for cognitive impairment in the general population because of insufficient evidence of efficacy. Cognitive impairment is three times more common in the dialysis population, affecting 16% to 38% of patients undergoing neuropsychological testing. Between 30% and 55% of kidney failure patients 75 years of age and older have cognitive impairment, as do 10% to 30% of young or middle-aged patients with kidney failure. "Mild cognitive impairment" generally describes impairment greater than that seen with normal aging but not meeting the criteria for dementia. Dementia is defined as progressive and chronic cognitive dysfunction with impaired memory and loss of function in at least one other cognitive domain such as reasoning, attention or executive function, orientation, language, or the skills required for planning and sequencing tasks. The decline observed from one's baseline cognitive level must be severe enough to interfere with independence and daily activities of living. Cerebrovascular disease with kidney failure likely contributes to the high rate of cognitive decline and dementia. Additional risk factors for dementia include anemia and albuminuria, age, nonwhite race, and female gender. Because of the high incidence of cognitive impairment in dialysis patients, screening may be useful for decision making, identifying potentially treatable causes, and possibly improving outcomes. Most important, recognizing cognitive impairment can serve as an impetus and direction for ACP with dialysis patients and their families.

Many screening tests for dementia exist. The use of such tests will depend on the clinical condition being considered, the time available for testing, and the frequency of anticipated testing. Although the Mini-Mental State

Examination (MMSE) is the best known of the screening tests, it does not evaluate executive function, and because deficits in executive function are a feature of vascular dementia, the MMSE is probably not the screening test of choice in dialysis patients in whom vascular dementia may be likely. The Montreal Cognitive Assessment (MoCA) has shown the greatest performance in predicting cognitive impairment in with CKD. The MoCA is easy for both patients and providers to use, is widely available, and is inexpensive. Most screening tests are sensitive but lack specificity. Uremia, delirium, and depression should be excluded as reversible treatable causes of cognitive impairment before diagnosing dementia.

Depression

Depression occurs in 20% to 30% of dialysis patients, impacting quality of life, adherence with treatments, functional status, and symptoms such as pain. Higher mortality rates and more frequent hospitalizations are seen in depressed dialysis patients. The American Preventive Task Force recommends screening for depression in the general population when staff-assisted depression care supports are in place (grade B evidence). In the United States, there is a Centers for Medicare & Medicaid Services mandate to screen dialysis patients for depression as part of quality care.

Vision

Ocular diseases such as cataracts, optic neuropathy, macular degeneration, subconjunctival calcification, and microvascular and diabetic retinopathy occur more commonly in CKD patients. Regular ophthalmologic examination and monitoring may prevent complications such as retinal detachment, hemorrhage, and vision loss. Patients with diabetes should continue to have regular eye examinations and treatment for retinopathy. Heparin anticoagulation during HD is considered safe without a higher risk of retinopathy.

Hearing

Sensorineural hearing loss occurs more commonly in dialysis patients, affecting 46% to 77% of these patients. Factors contributing to hearing loss in dialysis patients include hypertension, diseases such as vasculitis and Alport syndrome, electrolyte disturbances, exposure to radiocontrast and ototoxic medications such as aminoglycosides, and possibly vitamin D and nerve conduction dysfunction. High-frequency hearing loss is most common and is not related to dialysis vintage. Amplification with hearing aids is the primary treatment for hearing loss. Because Medicare does not cover the cost of hearing aids in the United States, financial constraints may complicate treatment for some dialysis patients. Vestibular dysfunction has also been seen in dialysis patients, especially in those exposed to high total doses of aminoglycosides.

Health Care Counseling

Exercise, weight loss and dietary counseling, tobacco use and cessation, sexual dysfunction, and contraception are all areas of preventive care addressed primarily by health care counseling. Each of these is relevant to kidney failure patients, and many are addressed in other chapters (see Chapters 34–36 on nutrition and Chapter 61 on rehabilitation.).

Exercise

Regular exercise can potentially improve physical functioning and control of diabetes and blood pressure and enhance psychosocial well-being and cardiovascular risk reduction, leading to better overall health-related quality of life. Nephrologists rarely assess dialysis patients' activity levels, and only 13% of dialysis patients report achieving the recommended level of physical activity (moderate intensity 3 days/week for 30 minutes each session). Lack of time and motivation, fatigue, and dyspnea are common barriers to exercise among dialysis patients. Formal studies of exercise's effects on dialysis patients showed a 12% improvement in physical performance and health-related quality of life, most pronounced in patients with the lowest levels of function at the start of the study. Dialysis unit exercise programs may provide opportunities for regular activity that lead to better physical performance and functioning, in turn reducing the likelihood of frailty and falls. An enthusiastic and dedicated dialysis facility staff is integral to the success of such programs.

Obesity and Weight Loss

Obesity is an increasing problem in dialysis patients, affecting 30% of the population. Obesity can be a barrier to kidney transplantation and a factor associated with better survival in HD patients. There is limited information about successful weight loss programs in dialysis patients. Bariatric surgery is increasingly considered by morbidly obese patients and has been reported as a successful strategy in dialysis (pretransplant) patients, although the mortality rate was 3.5% higher in dialysis patients compared with patients without kidney failure.

Tobacco Use and Cessation

Although there is no information on smoking cessation among dialysis patients, in the general population, most adult smokers want to stop, and even brief, repetitive cessation counseling from health care providers is effective. Thus, routine inquiry and counseling about tobacco cessation should be incorporated into health care counseling for dialysis patients who smoke. In the general population, 30% of those who stop smoking used medications as a part of their cessation strategy. Dose reduction of bupropion to 150 mg every 3 days versus 150 mg daily in nondialysis patients is recommended

based on pharmacokinetic data. Varenicline should be dosed at 0.5 mg/day in dialysis patients.

Contraception and Sexual Dysfunction

Although sexual dysfunction is common in women (30%–80% experience) and men (70% reported erectile dysfunction) on dialysis, most patients do not discuss these issues with their nephrologists or other care providers. Because sexual dysfunction can negatively impact patients' quality of life, this area of health care counseling in dialysis patients likely deserves more attention (see Chapter 56).

Although kidney failure may be considered a relatively effective contraceptive because of low fertility in women on dialysis, pregnancy can occur, and thus, premenopausal women on dialysis should be counseled about the possibility of pregnancy and effective means of contraception, especially if they have regular menstrual periods. If conception is deemed possible, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be discontinued because of the risk of fetal malformations with their use at the time of conception. Available contraceptive methods include intrauterine devices (probably should be avoided in women on PD because of the risk of infection), barrier methods, and hormonal therapies. There is little information about specific contraceptive methods in women with kidney failure, but the risks and benefits of each in the general population likely also apply to dialysis patients.

Advance Care Planning and Palliative or Supportive Care

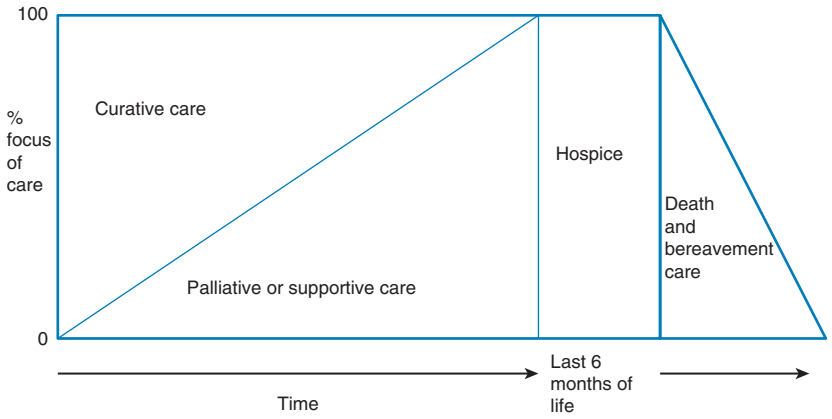
Advance Care Planning

ACP is a process of communication among patients, their families, and health care providers addressing goals of care within the context of the patient's values. Development and completion of advance directives (e.g., designation of a health care surrogate or proxy, living wills) may be one outcome of ACP but is not a requisite component of the ACP process. In many states, the Physician Orders for Life-Sustaining Treatment (POLST) form may be applicable and completed as desired by patients and families to ensure that a patient's wishes for life-sustaining care are followed. POLST forms are actual orders signed by a provider (physician or, in some cases, nurse practitioner or physician's assistant) and generally include sections on resuscitation status; guides for overall aggressiveness of care (maximizing comfort, wishes for selective treatments, complete life-sustaining care) in terms of intubation, vasopressors, antibiotics; and choices for medically administered nutrition such as feeding tubes and intravenous hydration. Designation of a surrogate decision maker and the patient or surrogate's signatures, as well as the signing health care provider, complete the document. In states accepting POLST forms, they are legally binding orders for care and the degree of that care as directed by the patient and their health care proxy.

ACP should be part of the routine and periodic care of each dialysis patient. The process of ACP should begin early in the course of CKD because ACP will be important in dialysis modality or conservative management selection when CKD stage 5 is reached. In addition, ACP will form the basis of the end-of-life care desired by the patient and their family and loved ones. For patients and families to make informed decisions about their care, including whether or not to begin dialysis, an estimate of prognosis is needed and should be provided by the nephrologist and/or primary providers discussing treatment, including options for dialysis. Tools exist for predicting survival on dialysis and use comorbidities such as the Charlson Comorbidity Index, patient age, serum albumin level, functional status, and the surprise question ("Would you be surprised if this patient died in the next 6 months?"), yielding a sensitivity of around 85%. When asked, most patients desire information on prognosis and require it to make informed decisions about their health care wishes. The Renal Physicians Association (RPA) Clinical Practice Guideline, *Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis*, is a clinically useful guide with toolkits to aid nephrologists in these aspects of care.

Supportive (Palliative) Kidney Care

Although supportive care is not classically defined as preventive care, in many respects, it is since anticipating and treating symptoms, fostering ACP, and planning for end-of-life care are the primary tenets of supportive care and represent opportunities for preventive care. Supportive care is appropriate for anyone with a chronic illness and should begin early in the course of that illness, accompanying curative care (Fig. 62.1). The increasingly elderly CKD population is focusing attention on conservative (no dialysis) care for some patients, and supportive care is clearly indicated for this group, as well as for dialysis patients, with their high symptom burden. Time-limited trials of kidney replacement therapy are advocated in cases of unclear patient and family wishes and prognoses. End-of-life care is one aspect of supportive care that includes hospice care, which is appropriate for any patient thought to have 6 months or less of remaining life. Hospice has been underused in kidney failure patients but is appropriate for any patient withdrawing from dialysis and those in CKD stage 5 opting out of dialysis. Some are advocating consideration of "palliative dialysis" for patients unwilling or not ready to stop dialysis. Involvement of palliative care specialists when available is encouraged, particularly by nephrologists and dialysis care providers with little experience in kidney supportive care. The Coalition for Supportive Care of Kidney Patients (www.kidneysupportivecare.org) and the RPA Clinical Practice Guideline, *Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis*, are invaluable resources for supportive care for CKD and kidney failure patients.



• **Fig. 62.1** Palliative care can be provided simultaneously with curative care. End-of-life and hospice care are components of palliative care, with hospice care occurring in the last 6 months of life. Bereavement care for the family and loved ones extends beyond the death of the patient. (Adapted from Lynn J. Living long in fragile death: the new demographics shape end of life care. *Hastings Center Rep.* 2005;Spec No:S14-S18.)

Monitoring: Lipids, Glucose, Anemia, and Bone and Mineral Disorders

Monitoring disease states and control of therapeutic interventions is another aspect of preventive care. In the case of kidney failure patients, anemia and bone and mineral disorders are monitored routinely in dialysis units (see Chapter 37). Chapter 49 reviews monitoring needs in patients with diabetes, which includes glucose control and the complications of diabetes such as retinopathy and neuropathy. Chapter 48 discusses monitoring and managing lipid disorders. In addition, dialysis accesses are monitored for function and complications, and these issues are reviewed in the relevant chapters (see Section II).

Recommended Reading

Burgner A, Hladunewich MA. Contraception and CKD. *Clin J Am Soc Nephrol.* 2020;15(4):563–565.

A review of the contraceptive options for women with CKD.

Butler AM, Olshan AF, Kshirsagar AV, et al. Cancer incidence among US Medicare ESRD patients receiving hemodialysis 1996–2009. *Am J Kidney Dis.* 2015;65(5):763–772.

Using the Medicare claims base, incidence rates of cancer in HD patients were defined for the years 1996 to 2009. The 5-year cumulative incidence rate of any cancer was 9.46%. Risk was highest for cancers of the kidney or renal pelvis and bladder (standardized incidence ratios, 4.03 and 1.57, respectively).

Celebi-Onder S, Schmidt RJ, Holley JL. Treating the obese dialysis patient: challenges and paradoxes. *Semin Dial.* 2012;25:311–319.

This review of obesity in dialysis patients addresses outcomes and treatments, including medications and bariatric surgery.

Choudhury D, Luna-Salazar C. Preventive health care in chronic kidney disease and end-stage renal disease. *Nat Clin Pract Nephrol.* 2008;4(4):194–206.

This paper reviews issues of preventive health care in CKD and ESRD, including prophylaxis for infections, TB, immunizations, monitoring and management of diabetes and lipid abnormalities, and cancer screening. The authors recommend appropriate preventive practices.

Davison SN, Levin A, Moss AH, et al. Executive Summary of the KDIGO Controversies Conference on Supportive Care in CKD: developing a road map to improving quality care. *Kidney Int.* 2015;88:447–459.

A summary of a conference addressing all aspects of supportive care in CKD, including ACP, symptom assessment, and management, prognosis.

Drew DA, Tighiouart H, Rollins J, et al. Evaluation of screening tests for cognitive impairment in patients receiving maintenance hemodialysis. *J Am Soc Nephrol.* 2020;31(4):855–864.

A study of the screening tests for cognitive impairment in dialysis patients who found MoCA to be the most appropriate screening tool.

Holley JL. General medical care of the dialysis patient: core curriculum 2013. *Am J Kidney Dis.* 2013;61:171–183.

This is part of the core curriculum series in nephrology, reviewing immunizations, cancer screening, health care counseling, and ACP in dialysis patients.

Johansen KL. Exercise in the end-stage renal disease population. *J Am Soc Nephrol.* 2007;18:1845–1854.

This review of exercise in ESRD patients discusses the effects of aerobic and resistance exercise, as well as the risks of exercise, and argues that exercise should be incorporated into the general care of ESRD patients.

Johansen KL, Chertow GM, Jin C, et al. Significance of frailty among dialysis patients. *J Am Soc Nephrol.* 2007;18:2960–2967.

The prevalence and predictors of frailty were assessed in a cohort of 2275 patients from the Morbidity and Mortality Wave 2 Study. Two-thirds met the definition of frailty, which was a composite construct incorporating poor self-reported physical functioning, exhaustion or fatigue, low physical activity, and undernutrition. Older age, female gender, and being on HD were independently associated with frailty. Frailty was associated with mortality with a hazard ratio of 2.24.

Li NC, Thadhani RI, Reviriego-Mendoza M, Larkin JW, Maddus FW, Ofsthun NJ. Association of smoking status with mortality and hospitalization in hemodialysis patients.

Am J Kidney Dis. 2018;72(5):673–681. *A retrospective review of over 22,000 patients (13% smokers) showed increased mortality and hospitalization in those who smoked. The highest mortality was in the heaviest smokers, with an HR of 141. Former smokers, diabetics, and younger smokers also had higher mortality.*

Renal Physicians Association. *Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis: Clinical Practice Guideline.* 2nd ed. Rockville, MD: RPA; 2010.

This is the most comprehensive guideline on palliative are issues related to dialysis. It contains specific evidence-based recommendations as well as helpful tool kits for nephrologists and dialysis care providers.

Yasin S, Holley JL. When ESKD complicates cancer screening and cancer treatment hemodialysis. *Semin Dial.* 2020;33(3):236–244.

A review of cancer incidence, screening, and treatment in ESKD patients.

SECTION 6

Systems Management for the Care of Dialysis Patients

63

Ethical Considerations in the Care of Dialysis Patients: The New Paradigm

ALVIN H. MOSS, MD, FACP, FAAHPM

Ethics in the care of patients is about doing the right and good thing. Nephrologists want to do the right thing and treat their patients ethically, but unfortunately, most have not received formal training in the ethics of dialysis patient care. Historically, dialysis patient care has been disease oriented and focused on laboratory indicators and survival as measures of quality of care. There is a relatively new recognition, as Allen Nissenson has written, that the nephrology community needs to shift the quality paradigm to what matters most to patients. As opposed to disease-oriented care, this new paradigm is patient centered!

Commentators on this shift have noted that the ethics of dialysis patient care is evolving from an emphasis on the ethical principles of beneficence and nonmaleficence—which fail to take account of patient values—to one in which the emphasis is on what is most important to patients. The ethical principle grounding this approach is respect for patient autonomy, which forms the legal basis for patient self-determination in decision making. As part of its recommendations for high-quality care in the 21st century, the Institute of Medicine (IOM) (now the National Academy of Medicine) recommended that medical treatment be patient centered. They defined patient-centered care as that which is responsive to and respectful of patients' values, preferences, and goals.

In practice, patient-centered care is implemented using the process of shared decision making. The American Society of Nephrology (ASN) and the Renal Physicians Association (RPA) have noted that shared decision making is the recognized preferred model for medical decision making because it addresses the ethical need to fully inform patients about the risks and benefits of treatments, as well as the need to ensure that patient's values and preferences play a prominent role. The ASN stated in the Choosing Wisely Campaign that maintenance dialysis should not be initiated without ensuring that a shared decision-making process between patients, their families, and their physicians has occurred.

The ASN and the RPA, in their clinical practice guideline *Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis*, recommended a seven-step process for ethical decision making. The first step is to identify the ethical questions (Table 63.1). Ethical questions ask what should or ought to be done. In the care of dialysis patients, the following ethical questions are particularly relevant: Who should and **should not** receive dialysis? On what basis should decisions about kidney replacement therapy and modality be made? When should a time-limited trial of dialysis be used? When should palliative care consultation be considered? When should palliative dialysis be offered? When should stopping dialysis be considered? How should a nephrologist respond to a patient's request to stop dialysis? How should a patient who stops dialysis be treated? When should a dialysis patient be referred to hospice?

Who Should and *Should Not* Receive Dialysis?

The ethical question in the 1960s "Who should be dialyzed?" morphed in the 1990s into "Who should *not* be dialyzed?" In the 1960s, it was unthinkable that patients with diabetes or older than the age of 75 would be candidates for dialysis. In 2020, patients with diabetes constituted 45% of incident dialysis patients, and patients older than the age of 75 are the fastest-growing age group in the dialysis population. The growth of the dialysis population had far exceeded the estimates when the Medicare End-Stage Renal Disease (ESRD) Program was established by Congress in 1972.

In the 1960s, the Admissions and Policy Committee of the Seattle Artificial Kidney Center decided who received access to dialysis and lived and who was denied access to dialysis and died. The straightforward answer to the question "Who should receive dialysis?" from an ethical perspective is that patients with medical indications for dialysis for whom the burdens are likely to outweigh the benefits and who consent to dialysis should receive it. The answer becomes more complicated for a number of reasons. First, not all patients with stage 5 chronic kidney disease (CKD) and an estimated

TABLE 63.1 The Seven-Step Process of Ethical Decision Making in Patient Care

1. What are the ethical questions?
2. What are the clinically relevant facts?
3. What are the values at stake?
4. List options. What could you do?
5. What should you do? Choose the best option from the ethical point of view.
6. Justify your choice. Refer back to the values and give reasons why some values are more important in this case than others.
7. How could this ethical issue have been prevented? Would any policies, guidelines, or practices be useful in changing any problems with the system?

Reproduced with permission from the Renal Physicians Association. *Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis*. 2nd ed. Rockville, MD: Renal Physicians Association; 2010.

glomerular filtration rate less than 10 mL/min is certain to benefit from dialysis. There is accumulating evidence that stage 5 CKD patients older than the age of 75 with significant comorbidities may not survive any longer with dialysis than without it. The level of this evidence has risen to the point where the second edition of the clinical practice guideline *Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis* recommends an informed consent conversation in which patients receive information about their diagnosis, prognosis, and all treatment options before a decision about dialysis is made. Similarly, the ASN, in its Choosing Wisely Campaign, identified that one of the five things physicians and patients should question is the possible limited benefit of dialysis to certain older patients. In its Choosing Wisely announcement on April 4, 2012, the ASN stated, "Don't initiate chronic dialysis without ensuring a shared decision-making process between patients, their families, and their physicians.… Limited observational data suggest that survival may not differ substantially for older adults with a high burden of comorbidity who initiate chronic dialysis versus those managed conservatively."

The clinical practice guideline also identified other groups of patients who should *not* receive dialysis: patients with decision-making capacity who, being fully informed and making voluntary choices, refuse dialysis or request that dialysis be discontinued; patients who no longer possess decision-making capacity who previously indicated refusal of dialysis in an oral or written advance directive; patients who no longer possess decision-making capacity with properly appointed legal agents who refuse dialysis for them or request that it be discontinued; and patients with irreversible, profound neurologic impairments such that they lack signs of thought, sensation, purposeful behavior, and awareness of themselves and the environment.

The guideline also recommended other patients for whom strong consideration should be given to not providing dialysis, that is, those who have a terminal illness from a non–kidney-related cause. For example, a patient who is dying from metastatic cancer for which no further chemotherapy or radiation therapy is being offered because of a low likelihood of benefit should, in most circumstances, not be started on dialysis. The potentially longer survival time that dialysis might afford is likely to be at the expense of a greatly diminished quality of life with significant pain and suffering as the cancer spreads. This same conclusion also could be reached for patients with end-stage heart or lung disease who, despite the provision of dialysis, might have severe progressive shortness of breath, pain, and a greatly diminished quality of life.

There are also patients whose medical condition precludes the technical process of dialysis because the patients are unable to cooperate with it, for example, a patient with advanced dementia who can only be restrained with great difficulty from pulling out his dialysis needles or catheter or a patient who because of severe cardiovascular instability experiences refractory hypotension during dialysis with loss of consciousness and seizures. Fortunately, the clinical practice guideline identifies these categories of patients and provides practical strategies for deciding with these patients and their legal agents about dialysis.

The publication of the first edition of the *Shared-Decision Making* clinical practice guideline in 2000 was in response to the report of the IOM Committee to Study the Medicare ESRD Program, which in its 1991 report recommended the development of a clinical practice guideline "for evaluating patients for whom the burdens of renal replacement therapy may substantially outweigh the benefits." The objectives for the first and second edition of the guideline were strongly motivated by ethical considerations: synthesize available research evidence as a basis for making recommendations about starting, withholding, continuing, and withdrawing dialysis; enhance understanding of the principles and processes useful for and involved in making decisions to withdraw or withhold dialysis; promote ethically as well as medically sound decision making in individual cases; recommend tools that can be used to promote shared decision making in the care of dialysis patients; and offer a publicly understandable and acceptable ethical framework for shared decision making among health care providers, patients, and their families. Table 63.2 presents the recommendations in this guideline.

Since the publication of the second edition of the clinical practice guideline in 2010 and the ASN Choosing Wisely recommendations in 2012, there have been additional major studies confirming the previous recommendations and documenting that older patients starting dialysis in the hospital undergo significantly higher intensity of treatment and shortened survival times with a high percentage of remaining life spent hospitalized. Noteworthy also is the accumulating evidence that older patients with CKD, especially those 75 or older, with a high burden of comorbidities and

TABLE 63.2 Recommendations from the Clinical Practice Guideline

Establishing a Shared Decision-Making Relationship

- Recommendation no. 1: Develop a physician–patient relationship for shared decision making.

Informing Patients

- Recommendation no. 2: Fully inform AKI, stage 4 and 5 CKD, and kidney failure patients about their diagnosis, prognosis, and all treatment options.
- Recommendation no. 3: Give all patients with AKI, stage 5 CKD, or kidney failure an estimate of prognosis specific to their overall condition.

Facilitating Advance Care Planning

- Recommendation no. 4: Institute advance care planning.

Making a Decision to Not Initiate or to Discontinue Dialysis

- Recommendation no. 5: If appropriate, forgo (withhold initiating or withdraw ongoing) dialysis for patients with AKI, CKD, or kidney failure in certain, well-defined situations.
- Recommendation no. 6: Consider forgoing dialysis for AKI, CKD, or kidney failure patients who have a very poor prognosis or for whom dialysis cannot be provided safely.

Resolving Conflicts About What Dialysis Decisions to Make

- Recommendation no. 7: Consider a time-limited trial of dialysis for patients requiring dialysis but who have an uncertain prognosis or for whom a consensus cannot be reached about providing dialysis.
- Recommendation no. 8: Establish a systematic due process approach for conflict resolution if there is disagreement about what decision should be made with regard to dialysis.

Providing Effective Palliative Care

- Recommendation no. 9: To improve patient-centered outcomes, offer palliative care services and interventions to all AKI, CKD, and kidney failure patients who suffer from burdens of their disease.
- Recommendation no. 10: Use a systematic approach to communicate about diagnosis, prognosis, treatment options, and goals of care.

AKI, Acute kidney injury; *CKD*, chronic kidney disease.
Reproduced with permission from the Renal Physicians Association. *Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis.* 2nd ed. Rockville, MD: Renal Physicians Association; 2010.

poor functional status who opt for medical management without dialysis may have a life expectancy and quality of life comparable to those who initiate dialysis therapy.

On What Basis Should Decisions About Kidney Replacement Therapy and Modality Be Made?

The clinical practice guideline and the ASN Choosing Wisely Campaign recommend a shared decision-making approach for making decisions about dialysis. Shared decision making is the recognized preferred model because it addresses the ethical need to fully inform patients about the risks and benefits of treatment, as well as the need to ensure that a patient's values and preferences play a prominent role. In shared decision making, the nephrologist is the expert in the patient's diagnosis, prognosis, and treatment alternatives, and the patient is the expert in their own history, values, and goals. In the process of shared decision making, physicians and patients reach an agreement on a specific course of treatment and share responsibility in the decision based on an understanding of the patient's overall condition and values. Shared decision making is appropriate for making decisions about starting, continuing, and stopping dialysis. Shared decision making achieves the goal of the IOM's 2001 report *Crossing the Quality Chasm: A New Health System for the 21st Century* by facilitating individualized, patient-centered care. The IOM defined "patient centered" as "providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions." In fact, shared decision making has been described as the "pinnacle" of patient-centered care. Unfortunately, data from numerous studies of dialysis patients performed between 2006 and 2013 show that shared decision making has been poorly integrated into the process of dialysis initiation for many patients. There is the expectation that dialysis decision making will improve as the recommendations of the ASN and RPA are implemented through the use of decision aids incorporating decision science.

When Should a Time-Limited Trial of Dialysis Be Used?

Time-limited trials of dialysis are specifically recommended when the benefit to a particular patient of dialysis is uncertain. The nephrologist may recommend dialysis, and the patient may be hesitant to begin it, or the opposite situation may be the case in which the nephrologist doubts the benefit of dialysis to the patient but the patient or the patient's family requests that dialysis be initiated. In both of these situations, a time-limited trial of dialysis may promote more informed shared decision making and help to resolve conflict about the dialysis decision. Both the nephrologist and the patient (or the patient's legal agent if the patient lacks decision-making capacity) will see how the patient tolerates dialysis and if the patient's overall condition improves with it. Before a time-limited trial of dialysis is begun, the length of the trial and the parameters to be assessed during and at the completion of the trial should be agreed upon so that at the conclusion of the trial, the decision about whether dialysis should be continued can be reached according to the predefined parameters (Table 63.3). Interestingly, in a 2005 survey of the RPA nephrologist membership, nephrologists who had been in practice longer and who were knowledgeable of the RPA and the ASN *Shared-Decision Making* guideline published in 2000 reported greater preparedness to make end-of-life decisions and use time-limited trials of dialysis. At the initiation of a time-limited trial, it is important for the nephrologist to specify that if the predetermined outcomes are not achieved, dialysis will be stopped, and the focus of the patient's care will be changed to intensive palliative care in which the goal will be the patient's comfort.

TABLE 63.3 Implementing a Time-Limited Trial of Dialysis

After Initiation of Time-Limited Trial

- Provide patient/family/legal agent regular updates
- Review progress regularly with other teams
  - Remain on the same page
  - Reach a shared agreement on plan for time-limited trial
- Set a date, time, and location for meeting after time-limited trial

At the Conclusion of Time-Limited Trial

- Continue renal replacement therapy if the patient improved according to goals
- Negotiate new time-limited trial if appropriate
- If the patient did not improve or deteriorated, pursue palliative care
- Transition to hospice as appropriate

Depending on the patient's condition, a transition to hospice may be appropriate.

When Should Palliative Care Consultation Be Considered?

Palliative care consultation has been documented to improve pain and symptom management and clarify goals of care. It has been especially helpful in assisting with decision making when there is conflict with regard to whether to start or continue dialysis. Often, a patient or family wants an older patient who is predictably a poor candidate for dialysis to start it or the family of a patient who is failing to thrive on dialysis wants to continue it.

Despite the fact that a growing body of evidence supports the use of inpatient palliative care consultation to promote patient-centered care for patients with end-stage kidney disease and to improve their experience of care at the end of life, palliative care consultation is infrequently requested for them. In one large study of older seriously ill dialysis patients with multiple comorbidities, less than 1% of dialysis patients who were hospitalized for more than 2 days received consults. When they were performed in patients who died during the hospitalization, the length of stay was shorter, and the costs of care were less. When the patient lived to discharge, the referral rate to hospice was higher, and the readmission rate was lower. Researchers have urged routine screening at hospital admission for identification of dialysis patients who could potentially benefit from inpatient palliative care consultation so that they would receive less unwanted aggressive and invasive care at the end of life.

When Should Palliative Dialysis Be Offered?

The patient-centered option of palliative dialysis for patients in their final year of life has garnered increasing attention. It has been defined as a transition from a conventional disease-oriented focus on dialysis as rehabilitative treatment to an approach prioritizing comfort and alignment with patient preferences and goals of care to improve quality of life and reduce symptom burden for maintenance dialysis patients in their final year of life. It is less concerned about measures of dialysis adequacy and conforming to laboratory test normal ranges and more attuned to patient comfort and quality of life with fewer medications and dietary restrictions. Concurrent hospice and palliative dialysis, regardless of the terminal diagnosis, represents a more patient-centered approach for those dying patients who want to be alive for a particular life event (wedding of a family member or the birth of a grandchild). Policies that flexibly help achieve patient-centered goals that enhance quality of life should be the ultimate aim of any public policy for supportive care of patients with kidney failure. Centers for Medicare and Medicaid Services (CMS) regulations will

need to be changed to allow patients who wish to continue dialysis under the Medicare Dialysis benefit while accessing the Medicare Hospice benefit. Also, quality measurements under the ESRD Quality Incentive Program for terminally ill dialysis patients will need to be developed that are separate from the current one-size-fits-all approach.

When Should Stopping Dialysis Be Considered?

Strong consideration should be given to stopping dialysis when the goals for which the patient started dialysis are no longer being accomplished. The U.S. Renal Data System reports that withdrawal from dialysis is the second most common reason for dialysis patient death, and the most common reason for withdrawal of dialysis is failure to thrive. An acute medical complication such as a stroke has been found to be the second most common reason for dialysis withdrawal. Common clinical scenarios in which patients or their family members make a decision to stop dialysis include accelerating comorbid illnesses, often with increased frequency of hospitalizations and loss of cognitive function with progression to severe cognitive impairment. A 2014 article by Schmidt, "Dying on Dialysis: The Case for a Dignified Withdrawal," provides a comprehensive checklist for implementation of dialysis withdrawal in patients who are failing to thrive on dialysis.

How Should a Nephrologist Respond to a Patient's Request to Stop Dialysis?

Although most dialysis centers have one or more patients who withdraw from dialysis each year, the majority of nephrology fellows report that they have not been taught how to respond to a patient's request to stop dialysis. The *Shared Decision-Making* guideline recommends a systematic approach to responding to such a request (Table 63.4), which

TABLE 63.4 Responding to a Patient's Request to Stop Dialysis

- Assess the patient's decision-making capacity and whether it is compromised by major depression, encephalopathy, or another disorder. Determine whether the patient's perceptions about dialysis and potential quality and quantity of life are accurate. Does the patient understand what will happen if dialysis is stopped?
- Does the patient really mean what they say, or is the decision being made to get attention, control, or help?
- Are there changes that might improve the patient's quality of life, and is the patient willing to continue dialysis while they are being made to see if their quality of life improves?
- Determine the reasons or conditions underlying the patient or surrogate request for withdrawal of dialysis. Such an assessment should include specific medical, physical, spiritual, and psychological issues, as well as interventions that could be appropriate.
- Identify potentially treatable factors such as the following:
  - Underlying medical disorders, including the prognosis for short- or long-term survival on dialysis
  - Difficulties with dialysis treatments
  - The patient's assessment of their quality of life and ability to function
  - The patient's short- and long-term goals
  - The burden that costs of continued treatment, medications, diet, and transportation may have on the patient, family, and others
  - The patient's psychological condition, including depression or conditions or symptoms that may be caused by uremia
  - Undue influence or pressure from outside sources, including the patient's family
  - Conflict between the patient and others
  - Dissatisfaction with the dialysis modality, the time, or the setting of treatment
- Depending on the assessment of potentially treatable factors, recommend psychiatric treatment or refer for counseling.
- Encourage the patient (if they have decision-making capacity) to discuss reasons for dialysis withdrawal with their family or support system.
- If a fully informed patient with capacity who has been offered or undergone treatment for potentially reversible factors still persists in the request for dialysis withdrawal, the patient's request should be honored to respect patient autonomy.
- If the patient lacks decision-making capacity, determine if the surrogate is making decisions according to the patient's prior expressed wishes for their current condition or according to what the surrogate determines to be the patient's best interest. If either is the case and there are not potentially treatable factors that could improve the patient's quality of life, agree to the request to respect the patient's autonomous decision when they had capacity or to prevent harm from a life in which there is suffering prolonged by dialysis.

determines the reasons or conditions underlying the request; assesses the medical, psychological, social, and spiritual motivations for such a request; and identifies what interventions could be undertaken to address the factors motivating the request. Determination of the patient's decision-making capacity and ruling out depression or encephalopathy are important first steps in the evaluation.

How Should a Patient Who Stops Dialysis Be Treated?

Patients who stop dialysis should be informed of their options for care, including palliative care and hospice, and be treated according to their values and preferences for type of treatment and site of treatment (Table 63.5). The average dialysis patient dies about 8 days after dialysis withdrawal, and 94% are dead within 1 month. For this reason, referral to hospice, if desired by the patient, should be made immediately at the time of dialysis withdrawal. Many hospices are willing to meet with the patient and family before formal admission to hospice to provide information. Advance care planning, including completion of advance directives, a do-not-resuscitate order, and Physician Orders for Life-Sustaining Treatment (POLST) Paradigm orders (if available in the state where the patient is being treated) is key to ensuring that everyone knows the plan of care and that the patient receives their desired treatment at the end of life.

TABLE 63.5 Comprehensive Treatment of a Patient Who Stops Dialysis

- Meticulous pain and symptom assessment and management
- Psychological, social, and spiritual support to the patient and family
- Shared decision making for informed consent on the patient's preferred treatment in the dying process and site of death
- Inclusion of family and legal agent in discussions
- Completion of advance directive specifying patient's preferred decision maker when incapacity occurs and preference for goals of care focused on comfort
- Completion of Physician Orders for Life-Sustaining Treatment (POLST) Paradigm medical orders (in states where available) specifying do not resuscitate (DNR) and comfort measures without readmission to the hospital except if patient cannot be kept comfortable at home
- DNR order and do not hospitalize order except for comfort in states without POLST Paradigm form
- Referral to hospice with the patient's permission
- Bereavement support for family after the patient's death
- Dialysis center annual memorial service for families of patients who stop dialysis

When Should a Dialysis Patient Be Referred to Hospice?

The family perspective is that hospice uses a patient-centered approach and provides the best quality of end-of-life care. Compared to those treating patients in hospitals or nursing homes, families have noted that hospice personnel is more respectful, attend more closely to pain and symptoms, and communicate more explicitly about what to expect and when to expect it so that the family can plan and cope. Nonetheless, it is clear from hospice utilization statistics that current policies result in underutilization for dialysis patients and hinder them from receiving hospice services. A decade ago, less than 14% of reported deaths among kidney failure patients received hospice care compared with more than 50% of persons with cancer, and only 3% received concurrent hospice and dialysis care. The situation has improved, with 27% of Medicare ESRD decedents using hospice in 2015. This is still just half of the 50.4% rate for all regular Medicare beneficiary decedents in 2015. Rates of both end-of-life hospitalization and hospice use vary widely by state, suggesting that it is not just patient preference driving utilization but also factors amenable to policy influence, such as capacity and practice patterns. In 2015, hospice use was much higher for those who discontinued dialysis versus those who did not (62% vs. 16%), showing how limited access to concurrent dialysis and hospice is. Even when patients stop dialysis, approximately 40% are referred to hospice within just 3 days of death. This is too short a time frame for hospices to be able to address patients reliably and family psychosocial and spiritual issues and for the patient's pain and symptoms to be well managed.

Current hospice coverage for patients with kidney failure in the United States is confusing and is inconsistently applied. Many hospices refuse to accept a patient with kidney failure under the Medicare hospice benefit for a terminal diagnosis other than kidney failure, even though the patient could continue to use the ESRD Medicare benefit for continuing dialysis. If hospice benefits are based on kidney failure as the terminal diagnosis, the hospice must provide coverage for all ESRD care, including dialysis, and the Medicare ESRD benefit ceases. For many reasons (financial and philosophical), a hospice may be unwilling to accept a patient in this situation. There is clearly a need for Medicare policy reform in this area to improve access to hospice for dialysis patients.

Summary

The answers, tables, and recommended readings prepare nephrologists to provide dialysis patient care with high ethical standards. For particularly complex cases in which there is conflict, nephrologists may want to request the assistance of an ethics or palliative care consultation service. Ethics consultation has been found to be helpful in identifying, analyzing, and resolving ethical dilemmas resulting in conflicts in patient care. Palliative care consultation has been found to be helpful in assisting with communication

about goals of care, methods of treatment, and pain and symptom management.

Recommended Reading

Butler CR, Mehrotra R, Tonelli MR, Lam DY. The evolving ethics of dialysis in the United States: A principlist bioethics approach. *Clin J Am Soc Nephrol.* 2016;11(4):704–709.

This article emphasizes that ethical principles are weighted differently depending on prevalent personal and societal values and presents a comprehensive ethical framework for evaluating appropriate use of dialysis that enables the clinician to systematically negotiate and optimize difficult ethical situations.

Chettiar A, Montez-Rath M, Liu S, Hall YN, O'Hare AM, Kurella Tamura M. Association of inpatient palliative care with health care utilization and post discharge outcomes among Medicare beneficiaries with end stage kidney disease. *Clin J Am Soc Nephrol.* 2018;13(8):1180–1187.

This article was one of the first to draw attention to the low utilization of palliative care consultation for dialysis patients and to provide a rationale for health care systems to expand access to inpatient palliative care for patients with ESRD to improve patient-centered care for them at the end of life.

Feely MA, Albright RC, Thorsteinsdottir B, Moss AH, Swetz KM. Ethical challenges with hemodialysis patients who lack decision-making capacity: behavioral issues, surrogate decision-makers and end-of-life situations. *Kidney Int.* 2014;86(3):475–480.

This article discusses the medical, ethical, legal, and psychosocial challenges in the care of dialysis patients with cognitive impairment and combative behavior who lack decision-making capacity and provides recommendations and highlights resources to assist nephrologists, dialysis personnel, ethics consultants, and palliative medicine teams in managing such patients to resolve conflict.

Germain MJ, Davison SN, Moss AH. When enough is enough: the nephrologist's responsibility to order dialysis. *Am J Kidney Dis.* 2011;58:135–143.

This article summarizes the importance of palliative medicine to the care of the patient throughout the continuum of kidney disease and provides an approach for decision making and treatment for patients who are not likely to benefit from dialysis therapy.

Grubbs V, Moss AH, Cohen LM, et al. Dialysis Advisory Group of the American Society of Nephrology. A palliative approach to dialysis care: a patient-centered transition to the end of life. *Clin J Am Soc Nephrol.* 2014;9(12):2203–2209.

This article highlights the importance of providing patient-centered palliative care for patients with advanced CKD and ESRD and draws attention to the fact that standard dialysis delivery may be inconsistent with the goals of care for many patients with ESRD. For patients in their final year of life, it urges consideration of a palliative approach to dialysis care, which focuses on aligning patient treatment with patients' informed preferences. This article describes a palliative approach to dialysis care and also reviews the barriers to integrating such an approach into the current clinical paradigm of care.

Moss AH. Ethical principles and processes guiding dialysis decision-making. *Clin J Am Soc Nephrol.* 2011;6:2313–2317.

This article describes the application of the ethical principles of respect for patient autonomy, beneficence, nonmaleficence, justice, and professional integrity and the ethical process of shared decision making in making decisions with patients and families about starting, withholding, continuing, and stopping dialysis.

O'Hare AM, Armistead N, Funk Schrag W, Diamond L, Moss AH. Patient-centered care: an opportunity to accomplish the "three aims" of the National Quality Strategy in the Medicare ESRD Program. *Clin J Am Soc Nephrol.* 2014;9:2189–2194.

This contribution presents the priorities of the Coalition for Supportive Care of Kidney Patients to achieve its vision of patient-centered care for CKD patients by using improved prognostic models and decision science to help patients, their families, and their providers better understand what to expect in the future; engaging patients and their families in shared decision making before the initiation of dialysis and during the course of dialysis treatment; and tailoring treatment strategies throughout the continuum of their care to address what matters most to individual patients.

Renal Physicians Association. *Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis.* 2nd ed. Rockville, MD: Renal Physicians Association; 2010.

This clinical practice guideline based on a systematic review of the medical evidence provides 10 recommendations and the rationale for each, along with strategies to improve the care of dialysis patients, including those at the end of life.

Rettig RA, Levinsky NG, eds. *Kidney Failure and the Federal Government*. Washington, DC: Committee for the Study of the Medicare ESRD Program, Division of Healthcare Services, Institute of Medicine. *National Academy Press.* 1991.

This study by a committee of the IOM was the first to recommend a clinical practice guideline for dialysis patient selection since it recognized that for some dialysis patients, the burdens of treatment outweigh the benefits.

Scherer JS, Holley JL. The role of time-limited trials in dialysis decision making in critically ill patients. *Clin J Am Soc Nephrol.* 2016;11(2):344–353.

This article describes how decisions about dialysis that were once based solely on survival are now nuanced by a patient's definition of quality of life, personal values, and short- and long-term prognoses. It presents the elements of a well-conducted time-limited trial that include assessment of prognosis, elicitation of patient values, strong communication skills, clear documentation, and often, appropriate integration of palliative care services. It notes that a well-conducted, time-limited trial can avoid interprofessional conflict and provide support for the patient, family, and staff.

Schmidt R, Moss AH. Dying on dialysis: the case for a dignified withdrawal. *Clin J Am Soc Nephrol.* 2014;9:174–180.

This article identifies the most common scenarios for patients who are dying on dialysis and provides a comprehensive checklist for implementation of compassionate dialysis withdrawal in patients who are failing to thrive.

Wong SP, Kreuter W, O'Hare AM. Treatment intensity at the end of life in older adults receiving long-term dialysis. *Arch Intern Med.* 2012;172:661–663.

This article compares the outcomes of older Medicare beneficiaries receiving long-term dialysis with those with cancer and congestive heart failure and finds that the end-of-life care is worse for dialysis patients, who spend twice as many days in the hospital during the last month of life, are three times more likely to undergo an intensive procedure during the hospitalization and are less likely to be referred to hospice and die at home.

Wong SPY, Kreuter W, O'Hare AM. Healthcare intensity at initiation of chronic dialysis among older adults. *J Am Soc Nephrol.* 2014;25:143–149.

This research reports the poor outcomes for older patients who start dialysis in the hospital after a more than 2-week admission and urges informed consent because for older CKD patients, quality of life may be more important than quantity of life.

64

Improving Outcomes for End-Stage Renal Disease Patients: Shifting the Quality Paradigm*

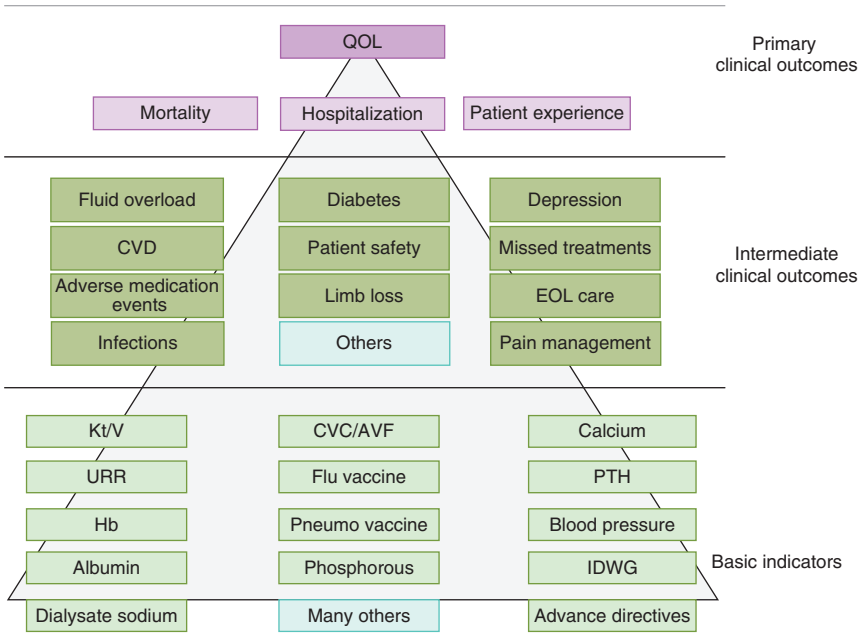
ALLEN R. NISSENSON, MD, FACP

Since the implementation of the End-Stage Renal Disease (ESRD) program entitlement in 1973, the program has been under the microscope, and rightfully so. Initially envisioned to provide needed coverage for a few thousand patients through Medicare, it was anticipated that the program would not only provide life-sustaining dialysis therapy but would also result in patients returning to full, active, productive lives, including a return to employment. Over the past nearly 50 years, however, the evolution of the ESRD program has been quite different, a fact that has been documented by the U.S. Renal Data System (USRDS). At the end of December 2017, there were more than 746,500 patients with ESRD in the United States, and although the growth rate of this population may be slowing, the complexity of the patients receiving this high-cost, technically complex treatment is increasing. The majority of patients have three or four comorbid conditions in addition to ESRD, with diabetes and hypertension causing ESRD in nearly two-thirds of patients and cardiovascular disease highly prevalent. Patients are receiving 8 to 10 different medications daily, and the current most common form of dialysis, thrice-weekly in-center hemodialysis, replaces the equivalent of 10% to 14% of small-solute removal compared with natural kidneys. The ability of conventional dialysis to remove the full range of toxins necessary to optimize health, including salt and water, is inadequate.

Mortality and hospitalization rates have improved significantly in ESRD patients over the past two decades. Unfortunately, however, ESRD patients continue to have high mortality and morbidity. Mortality remains greater than 16% annually overall and nearly 40% for patients new to dialysis, with an average of nearly two hospitalizations still occurring per patient per year. Although late-stage chronic kidney disease (CKD) and ESRD patients comprise just over 1% of all Medicare patients, they consume nearly 10% of the overall costs of Medicare, exceeding $50 billion.

Numerous publications and demonstration projects have pointed out the need to reexamine the approach that has been taken to improve clinical outcomes and constrain costs for this vulnerable population. Largely because of the USRDS and provider consolidation with the development of comprehensive administrative databases, U.S. ESRD patients are the most data-dense chronic disease population in the world. To date, quality improvement has been largely focused on biochemical or surrogate outcomes, as has been attempted with other disease states. However, there is an urgent need to move beyond such outcomes to focus on more patient-centric care, as emphasized by the Patient-Centered Outcomes Research Institute (PCORI). Clearly, reorganization of the care delivery system, focusing on care coordination, comorbidity management, and patient-centered care, can be effective in this population as demonstrated by Centers for Medicare & Medicaid Services (CMS) completed demonstrated projects and the preliminary results of the Comprehensive ESRD Care Initiative developed and overseen by the Center for Medicare and Medicaid Innovation (CMMI). Ironically, despite the clear value shown in the demonstration project and the CMMI projects for certain interventions such as oral nutritional supplements, dental care, transportation, and home health services in selected patients, such benefits are uncovered for the majority of ESRD patients still in the Medicare fee-for-service payment system. Although the pilot projects developed by CMMI, the ESRD Seamless Care Organization (ESCOs), have shown improved clinical outcomes and lower costs, the approach to evaluating and incentivizing quality remains problematic. In particular, the reliance on laboratory measures, the use of "public sector" metrics that are not appropriate for ESRD patients, and the lack of patient-reported outcomes metrics are among the continuing issues.

*Modified with permission from Improving outcomes for ESRD patients: shifting the quality paradigm. *Clin J Am Soc Nephrol.* 2014;9:430-434.



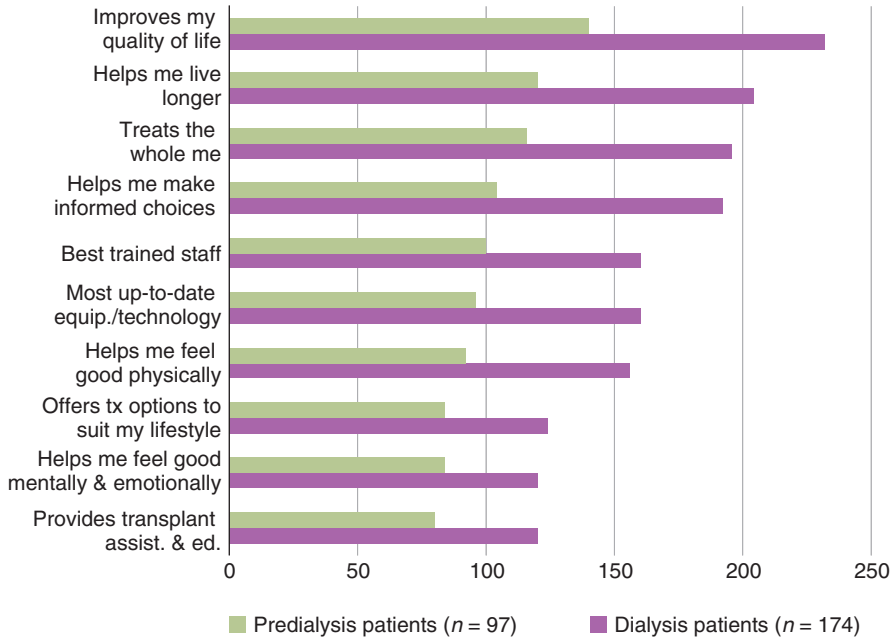
• **Fig. 64.1** The patient-centered quality pyramid. Fundamental outcomes are necessary but not sufficient to climb the pyramid through complex programs to achieve lower mortality rates, fewer hospitalizations, and enhanced patient experience of care. Ultimately, if successful, patients will achieve an improved QOL. *AVF*, Arteriovenous fistula; *CVC*, central venous catheter; *CVD*, cardiovascular disease; *EOL*, end-of-life; *Hb*, hemoglobin; *IDWG*, interdialytic weight gain; *PTH*, parathyroid hormone; *QOL*, quality of life; *URR*, urea reduction ratio.

The nephrology community should not wait for the final results of the CMMI ESCO initiative to act; these vulnerable patients deserve action now, which will improve outcomes as well as provide the good stewardship of resources of this large public program that the public expects. Recent publications show wide agreement within the nephrology community that care coordination incorporating nephrologist leadership is a promising approach to significantly improving outcomes. Care coordination as a delivery model is fundamental to improving outcomes by itself; it will not ensure the goal—improving the lives of patients with kidney disease—without consensus on the key clinical targets and metrics to drive this goal.

Although there is widespread recognition of the areas of clinical focus that are most likely to improve survival, morbidity, the patient experience, and overall quality of life, the ability of providers to deliver on these areas has been stymied by the lack of a unified conceptual framework for quality for ESRD patients and a well-meaning CMS Quality Improvement Program (QIP), which, unlike the approach advocated by VanLare and Conway at CMS, used primarily laboratory indicators, which in and of themselves are no longer the key drivers to improve the primary clinical outcomes significantly. Outcomes related to hospitalizations and mortality use standardized ratios, comparing actual with "expected" outcomes. The latter, however, is not based on transparent adjusters, and reliance on comorbidity data from the 2728 Medical Evidence forms adds to the inaccuracy.

We have therefore developed a patient-focused needs hierarchy meant to better describe and encourage the approach to patient outcomes that is the most likely to significantly improve the lives of patients with kidney disease (Fig. 64.1). As Stephen Covey, the business leader and author pointed out: "Begin with the end in mind." For patients with advanced kidney disease, the "end" is improving the quality of their lives. It should be noted that we use "quality of life" in this hierarchy because it is the term generally used as a key primary outcome in health care, although for the proposed paradigm, we define this somewhat more narrowly as aspects of improving the lives of kidney patients that can be impacted through improving mortality, lowering hospitalizations, and enhancing patients' experiences with treatment. Although some patients may state that they cherish length of life more than anything, the vast majority focus on the quality rather than the quantity of life as most important. We recently had an independent group carry out a survey of 271 patients (DaVita Kidney Care data on file, 2011), some on dialysis, some with advanced CKD. Fig. 64.2 clearly shows that patients want to live long lives, but more importantly, they want to have a high quality of life and be treated with compassion and respect. The value of specific clinical outcomes is less important to patients because they assume that competent dialysis facilities will provide safe and effective treatment or would not be allowed to function by Medicare. A study from Australia focused on patient priorities for research in CKD is consistent with these data.

So if one starts with the top of the hierarchy—the overarching goal to improve the lives of patients with kidney disease—it is necessary, if one is to accomplish this, to improve survival, decrease hospitalizations, and optimize patient experience with care, which are on the highest tier of our pyramid as primary clinical outcomes. Moving further down the hierarchy, there is a constellation of potential intermediate



• **Fig. 64.2** Survey of patients demonstrating that quality of life is the most important outcome to them. *Tx*, Treatment.

clinical outcomes, complex clinical areas, that if optimized, are most likely to drive the desired improvements in primary clinical outcomes. In the case of hospitalizations, for example, a recent analysis of claims data taken shows that cardiovascular disease, much caused or worsened by acute or chronic fluid overload, infection, and diabetes, accounts for the majority of hospitalizations (Fig. 64.3). Additionally, we believe that appropriate medication management is critically important if hospitalizations are to be avoided, but quantifying the contribution of medication errors and complications is not possible to tease out from claims data. Other potential intermediate clinical outcomes, such as depression and missed treatments, have been shown to impact primary outcomes as well. These intermediate clinical outcomes are the areas of care that currently drive hospitalizations, rehospitalizations, and mortality and contribute to a suboptimal patient experience.

The basic indicators form the lower layer of the hierarchy and are the ones that have largely preoccupied the renal community and regulators over the past decades. What we propose is that poor performance on these basic indicators will ensure poor, intermediate clinical outcomes. However, excellent performance on these indicators, as is currently the case for a number of these for most providers of care, has not resulted in significant improvements in intermediate or primary outcomes. Thus, excellent performance on the basic indicators is necessary but not sufficient to lead to excellent primary outcomes. The intermediate outcomes are more complex than the basic indicators, requiring systematic, organized clinical programs, multiple indicators, and often-fundamental changes in the culture of the dialysis facility and dialysis team if they are to be successfully improved.

How could this conceptualization of the clinical hierarchy for ESRD patients be put to practical use to drive quality improvement in a dialysis clinic as well as inform policymakers responsible for oversight of the ESRD program as well as the overall public programs, Medicare and Medicaid, that focus disproportionate resources on the complex, chronically ill? In the dialysis clinic, the interdisciplinary team, including nurses, dietitians, social workers, technicians, and the medical director, needs to be the engine that drives clinical quality. To this team, the hierarchy can help organize thinking and action by drawing an analogy to a basketball team, the ultimate goal for which is to win the game. The team must start with skilled players and execute on the fundamentals, namely, the basic indicators—dribbling, passing, shooting, blocking. But, mastering these fundamentals in no way ensures the game will be won. Instead, the players need to build on the fundamentals and evolve into more complex interactions—plays, offense, and defense. When these plays come together, the result is more offensive points, fewer defensive points, and ultimately the goal—the game is won. The analogy to this in the ESRD world is that when a facility has excellent scores on the basic indicators, it is time to move up to the big leagues by organizing the fundamentals into complex intermediate clinical initiatives on the way to achieving lower mortality rates, fewer hospitalizations, and better patient experiences and ultimately improving patient's lives.

Two major observations have significantly affected the way we perceive the basic, largely laboratory indicators in ESRD. First, we have a number of large prospective clinical trials that show us that what we may have observed about the achievement of certain basic biochemical markers and primary outcomes such as mortality and morbidity were not correct. Second, we have noted that many facilities have reached "clinical optimization" for many of the basic indicators. We use this term to indicate facility-level

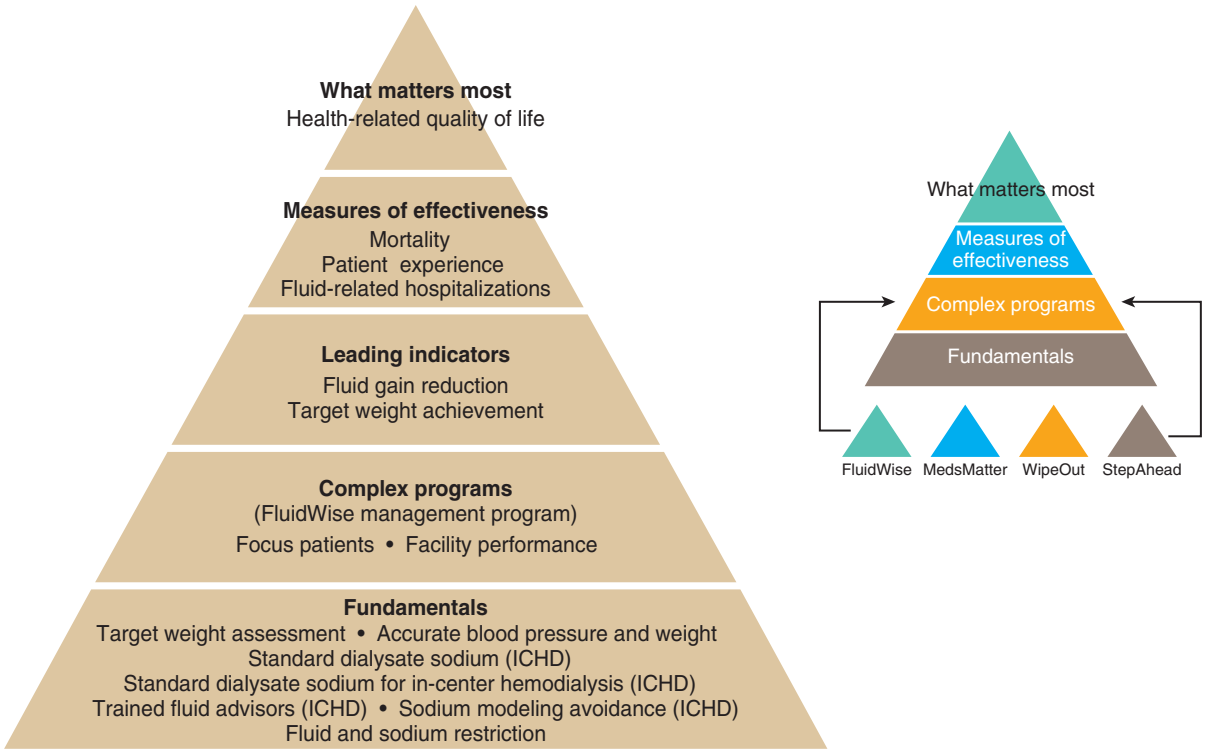
	Percent of Total Admissions
Fluid excess (directly and indirectly related)	30.4
■ CVD (controllable)	9.9
■ Fluid overload	6.5
■ Hypertension	5.3
■ CHF	4.0
■ Fluid and electrolyte disorders	2.7
■ CVD (non-controllable)	2.1
Infection (directly related)	19.9
■ Vascular access	10.4
■ Septicemia	5.5
■ Vaccine preventable pneumonia	4.0
Diabetes (directly related)	5.1
■ Diabetes	4.3
■ Diabetes-related amputation	0.9
Other	0.3
■ Depression	0.3
Total listed above	55.7
All additional causes (e.g., brain aneurysm)	44.3
Grand total	100.0

• **Fig. 64.3** The most common causes of hospitalizations in patients with end-stage renal disease based on claims data. *CHF*, Congestive heart failure; *CVD*, cardiovascular disease. (2009 USRDS data; DVA patients. Courtesy of Dr. Steven Brunelli.)

performance for a given indicator when the mean value is well into the target range and the performance variation is minimal among patients. Hemodialysis adequacy is a good example of clinical optimization based on recent QIP data, with nearly 98% of facilities achieving optimization using CMS definitions. Although it will remain important going forward to maintain clinically optimized performance on the basic indicators, future focus and investment in clinical programs should move up the pyramid to intermediate outcomes if we are truly to drive to improving patients' lives. What does this mean practically within a large dialysis organization? We have developed and successfully implemented programs to drive the basic indicators. As these basic indicators have moved to a state of clinical optimization, the corporate support shifts from program development to active surveillance of performance across the organization to a focus on outliers to ongoing watchful monitoring to prevent deterioration in performance. Proactive program development and resource allocation now go to the areas of intermediate outcomes that are the most impactful, in particular, fluid management, infection management, diabetes management, and medication management. The latter derive from claims data analyzed and published by Peer and the USRDS. This practical application of the conceptual pyramid drives other strategic decision making within the organization. For example, investment in new technology that specifically drives the key intermediary outcomes would have a higher priority than technology that addressed other aspects of care. In addition, areas of the organization that support the clinical care delivered, such as clinical laboratories and information technology, are using the clinical hierarchy prioritization scheme as they consider how best to provide the support needed to drive up the pyramid.

At the facility level, the hierarchy provides a powerful tool to ensure that the interdisciplinary team fully understands and embraces this new way of thinking about clinical outcomes. An example relates to a focus on the key secondary outcome of fluid management. This is a complex area on the surface, and because of its many components, it would be overwhelming to most dialysis facilities. By breaking it down using the hierarchy, however, it begins to be easier for facilities to tackle. In fact, for each such complex clinical program, we have built a program-specific pyramid, again emphasizing that each program can be thought of as composed of fundamental and more complex components. Underlying all of the components of "quality" in the pyramid is the commitment to optimizing the patient experience of care, developing metrics, and monitoring effectiveness using patient-reported outcomes (PROs). An example of a program-specific pyramid is provided in Fig. 64.4. We have used the pyramid approach in other areas as well, including medication therapy management, and recently have published this approach. We would use the generic pyramid and then the fluid-specific or other program-specific pyramids to work with teammates. In the case of fluid management, we would do this in the following way:

1. Explain and educate the teams in the facilities that appropriate attention to sodium, particularly avoiding sodium loading during dialysis from too high a dialysate sodium or use of sodium modeling, are basic components of a more complex program, fluid management, that is under the control of the dialysis facility.
2. If the facility is successful in impacting fluid management, in part through controlling sodium loading during dialysis, this will result in fewer hospitalizations, better survival, and a better patient experience.



• **Fig. 64.4** The quality pyramid for fluid management. *ICHD*, In-center hemodialysis. (From DaVita HealthCare Partners, Inc., with permission.)

3. If successful, the result will be the ultimate goal being achieved—improving the patient's life.
4. To succeed in optimizing fluid management, one uses the fluid pyramid, starting with the fluid fundamentals and proceeding up the fluid pyramid to more complex actions.

From the perspective of policymakers, the hierarchy clearly shows that the renal community is interested in patient-centered care—driving toward what is important to patients. It emphasizes that the basic indicators are important but that we now have a strong foundation and need to move to more impactful clinical programs to drive improvements in the primary outcomes. Policy decisions regarding quality incentives need to keep pace with this paradigm shift in clinical focus.

Such a framework is helpful in communicating the importance of the new programs and initiatives to a wide audience and helps to get health care delivery teams and patients aligned on program rationale. This allows population-based management programs to be successfully implemented to improve outcomes. Although clinicians know what is needed to improve the lives of patients with kidney disease, up to now, they have not had a conceptual framework to articulate this within their own organizations or externally, particularly to CMS. If key stakeholders can embrace such a common vision and share best practices and innovative ways to drive the secondary outcomes, it is likely that patients will see the benefits of moving the focus "up the pyramid," and that all will benefit as a result.

Recommended Reading

Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared to low hematocrit levels in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med.* 1998;339:584–590.

The seminal article demonstrating the impact of anemia and its treatment on survival in dialysis patients. Further illustration on the importance of maintaining solid fundamentals in the pyramid.

Centers for Medicare & Medicaid Services. Comprehensive ESRD Care Initiative. http://innovation.cms.gov/initiatives/comprehensive-ESRD-care/.

Explanation of the proposed ESRD care coordination program, being run through the CMMI Innovation.

Covey S. *The 7 Habits of Highly Effective People.* New York, NY: Simon and Schuster; 1989.

The guru of management here shares one of his seminal sets of guidelines.

Kidney Care Partners. Performance Excellence and Accountability in Kidney Care. http://www.kidneycarequality.com/.

The articulation by Kidney Care Partners of the progress and needs for focus on quality in the ESRD program.

Kimmel PL, Cukor D, Cohen SD, Peterson RA. Depression in end-stage renal disease patients: a critical review. *Adv Chronic Kidney Dis.* 2007;14:328–334.

Depression is clearly a complex issue, common in ESRD patients, that can impact mortality and hospitalization.

Maddux FW, McMurray S, Nissenson AR. Toward population management in an integrated care model. *Clin J Am Soc Nephrol.* 2013;8:694–700.

In this paper, the concept of population health and management is described as it relates to the care of kidney patients. This is not an area taught during Nephrology Fellowship programs.

Nissenson AR. Improving outcomes for ESRD patients: shifting the quality paradigm. *Clin J Am Soc Nephrol.* 2014;9:430–434.

The patient-focused quality pyramid concept as originally developed and described.

Nissenson AR, Deeb T, Franco E, et al. The ESRD Demonstration Project: what it accomplished. DaVita Inc. *Nephrol News Issues.* 2011;25:39–41.

A summary of the CMS demonstration project on care coordination for ESRD patients. This paper provides the outcomes for patients managed in this program by DaVita, demonstrating the significant clinical and financial benefits of this approach to delivering and funding care.

Nissenson AR, Maddux FW, Velez RL, Mayne TJ, Parks J. Accountable care organizations and ESRD: the time has come. *Am J Kidney Dis.* 2012;59:724–733.

An explanation of new approaches to organizing care for ESRD patients and encouraging nephrologists to understand and participate in such activities.

Obialo C, Hunt W, Bashit K, Zager P. Relationship of missed and shortened hemodialysis treatments to hospitalizations from a US dialysis network. *Clin Kidney J.* 2012;5:315–319.

An excellent study showing how adherence to the dialysis treatment is a key component driving survival and hospitalizations.

Parker T 3rd, Hakim R, Nissenson AR, Steinman T, Glassock RJ. Dialysis at a crossroads: 50 years later. *Clin J Am Soc Nephrol.* 2011;6:457–461.

An opinion piece by senior nephrologists published to help accelerate the movement to improve outcomes for patients with CKD or ESRD.

Parker TF 3rd, Straube BM, Nissenson A, et al. Dialysis at a crossroads—part II: a call for action. *Clin J Am Soc Nephrol.* 2012;7:1026–1032.

A follow-up to the initial paper published to stimulate move faster to improve outcomes for kidney patients. This paper includes specific recommendations for achieving this goal.

Patient-Centered Outcomes Research Institute. Homepage | PCORI.

A recent summary of the activities of PCORI, a new agency formed through the Affordable Care Act focused on pragmatic research based on patient-centered outcomes.

Roer D, Fukui M, Smith N, Nissenson AR, Becker BN. Current value-based care models need greater emphasis on specialty care. *Am J Accountable Care.* 2019;7(3):24–29.

A review of the critical role of specialists in value-based care models, particularly for the complex chronically ill, such as patients with kidney disease.

Sauer P, Farrell R, Lazarus J. The ESRD Demonstration Project: what it accomplished. Fresenius Medical Care North America. *Nephrol News Issues.* 2011;25:37–38.

A summary of the Fresensius Medical Care (FMC) experience with the CMS demonstration project. Significant clinical and financial benefits are demonstrated in the FMC experience.

The United States Renal Data System 2019 Annual Data Report. *Epidemiology of Kidney Diseases in the United States.* Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2019. https://www.usrds.org/2019/view/USRDS_2019_ES_final.pdf.

The recent report of overall demographics and outcomes in the U.S. ESRD program.

Tong A, Sainsbury P, Carter SM, et al. Patients' priorities for health research: focus group study of patients with chronic kidney disease. *Nephrol Dial Transplant.* 2008;23:3206–3214.

This paper documents that attaining a high quality of life is a key focus for patients.

VanLare JM, Conway PH. Value-based purchasing—national programs to move from volume to value. *N Engl J Med.* 2012;367:292–295.

Senior leaders at CMS provide an overview of the direction being pursued by the biggest public payer—Medicare.

Weinhandl E, Ameson T, St. Peter W. Clinical outcomes associated with receipt of integrated pharmacy services by hemodialysis patients: a quality improvement report. *Am J Kidney Dis.* 2013;724–733.

A clear demonstration that attention to medication management improves adherence to medications and leads to improved survival and fewer hospitalizations.

Wigneswaren J, St. Peter WL, Nissenson AR, et al. Redefining medication management in dialysis: a kidney pharmacy quality pyramid. *Kidney Med.* 2019;1(5):307–314.

Application of the clinical quality pyramid to medication therapy management.

Williams AW, Nesse RE, Wood DL. Delivering accountable care to patients with complicated chronic illness: how does it fit into care models and do nephrologists have a role? *Am J Kidney Dis.* 2012;59:601–603.

Another view of the emerging field of accountable care and care coordination in nephrology. This is a view from the American Society of Nephrology discussing the benefits and potential concerns with this approach to care.

65

Quality, Safety, Accountability, and Medical Director Responsibilities

JAY B. WISH, MD

Introduction

The challenges found in end-stage kidney disease (ESKD) facilities in the United States mirror fundamental shortcomings in the American health care system in general, as described in the Institute of Medicine (IOM) 2001 report *Crossing the Quality Chasm: A New Health Care System for the 21st Century*. The IOM concludes that "the American health care delivery system is in need of fundamental change." The IOM proposes six key goals for the 21st-century health care system: safe, effective, patient centered, timely, efficient, and equitable.

The IOM points out that much of the quality "chasm" that currently exists in health care delivery is due to misaligned incentives between health care systems, payers, medical professionals, patients, technology, education, and legal liability. Multiple interrelated dimensions of health care delivery must be addressed, improved, and aligned to improve the quality chasm. Several of these dimensions have immediate relevance to the care of dialysis patients and include quality, safety, and accountability.

Quality

Quality in health care has taken on increased importance over the past 2 decades as payers, regulators, and patients have all demanded an improved product from health care providers. In the 1980s and early 1990s, the emphasis was on *quality assurance*. However, traditional quality assurance activities were never embraced by physicians because quality assurance departments in hospitals were generally staffed by nurses involved in risk management and utilization review, which fostered the concept that quality assurance was a burdensome and intrusive function with little impact on patient outcomes. Although industry had successfully applied the principles of quality improvement for many years because of the opening of worldwide markets that forced manufacturers to focus on quality, American health care providers had been immune from competitive pressures until the increased penetration of capitated payment plans forced health care providers to lower costs and improve quality.

The principles of quality improvement are so intuitive that it is difficult to understand why physicians have been resistant to embracing them. Table 65.1 summarizes the benefits of quality improvement. Quality improvement is similar to the differential diagnosis of a medical problem. First, one builds a list of possible etiologies ("rule-outs"). Then one initiates testing or therapy to rule out each possibility until the diagnosis is confirmed. Finally, one checks the patient for evidence of improvement to validate that the diagnosis and choice of therapy were correct.

In quality improvement, a multidisciplinary team at the provider level examines an issue in which there is an opportunity for improvement. This might be a structural issue (e.g., staffing ratios or the water treatment system), a process issue (e.g., the drawing of postdialysis blood urea nitrogen levels or the administration of influenza vaccine), or an outcome issue (e.g., a high percentage of patients with low Kt/V or with dialysis catheters). The team then brainstorms to list the "differential diagnosis" classified by category, such as procedures, equipment, policies, staff factors, and patient factors. The team develops consensus on which one or more of these causes might be responsible for the suboptimal performance and then develops and implements a change in process to test whether this improves performance. Data collected before and after the process change are compared. If significant improvements in performance occur after the change, the process change is incorporated more widely.

Thus, the fundamental principles underlying quality improvement are (1) all work can be described as a process, (2) variation exists in every process, (3) the performance of processes can be measured, (4) measurement requires comparison, and (5) the goal is to reduce variation within acceptable limits by testing and validating the processes that produce the best results. Although the advancement of evidence-based medicine and the proliferation of clinical

TABLE 65.1 Benefits of Quality Improvement

Improved Patient Outcomes

- Decreased morbidity and mortality
- Improved quality of life
- Improved satisfaction

Improved Facility Outcomes

- Increased patient census
- Fewer absences for hospitalization
- Decreased mortality
- Increased market share
- Decreased costs
- Increased efficiency
- Improved employee retention and productivity
- Improved risk management
- Fewer regulatory hassles

Improved System-Wide Outcomes

- Decreased hospitalization expenses
- More cost-effective care
- Improved rehabilitation
- Contribution to evidence-based literature

practice guidelines have begun to clarify which care processes are likely to produce the best clinical outcomes; all providers have unique barriers to process improvement that must be identified at the facility level by individuals who know the processes best.

Ultimately, "care" represents a linkage of many processes, and the success of quality improvement initiatives requires the empowerment of those individuals "in the trenches." An obstacle to the successful implementation of a quality improvement culture is management failing to relinquish power to its employees and to trust its employees to effectively use the resources that have been put at their disposal to improve processes of care and patient outcomes. Quality improvement has been described as both "bottom-up" and "top-down." The top-down aspect means that management must commit itself at the highest level (e.g., board of directors, chief executive officer) to a quality improvement culture and allocate the resources necessary for a quality improvement program to succeed.

Successful quality improvement requires appropriate data management infrastructure to track processes and outcomes, education and training of staff in the principles and application of quality improvement techniques, providing employees with the protected time necessary to attend quality improvement meetings and to manage quality improvement data, and individuals in leadership positions emphasizing their commitment to quality improvement through their own actions and words. The bottom-up aspect of quality improvement means that it is ultimately the workers who execute the care processes on a daily basis and who are best qualified to examine which processes of care are most effective—identifying the barriers to improving outcomes and ultimately implementing changes in processes to overcome those barriers and to benefit patients.

Although the IOM has developed a somewhat arcane definition of health care quality ("the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge"), many health care providers (including physicians) may find it easier to relate to health care quality as a product delivered by a provider to a customer. This customer could be identified as the patient or the payer. As in other markets, the customer can and should articulate whether or not the product meets expectations.

The expectations of a payer such as Medicare are very clear and are contained in the Conditions for Coverage (CfC) for dialysis facilities. However, satisfying the CfC is merely meeting a minimum standard of care required of all dialysis providers and is quality assurance, not quality improvement. Because the ultimate goal of quality improvement is to improve outcomes for patients, the patient's perspective must be considered—and the use of patient satisfaction and quality of life instruments has become increasingly important to identify opportunities for process improvement, especially in the context of the ongoing paradigm shift to a more patient-centered health care delivery environment.

The development of a data management infrastructure is essential to the ability to compare a provider's own performance with others and with itself over time. Data are a cornerstone of quality improvement. An adequate data management infrastructure is essential to the development of inferences about causality and improved decision making that is ultimately based on evidence.

Another cornerstone of quality improvement culture is respect for the individual. Quality improvement projects succeed because they are owned and championed at the process level rather than the executive level. The culture of quality improvement requires a shift from management to leadership, from control to coaching, from resistance to openness to change, from suspicion to trust, from an internal focus to a customer focus, and to seeing people as resources rather than as commodities.

Physicians have traditionally resisted quality activities as second guessing by nonexperts and have almost invariably delegated quality activities to a head nurse or quality assurance coordinator. Quality improvement cannot be delegated. All individuals, especially those in leadership positions, must embrace it for it to succeed. The commitment of the nephrologist is particularly vital for quality improvement to succeed in the dialysis facility because the physician is a respected leader who sets an example by their own actions and because the physician is a central figure for

many of the care processes that ultimately impact patient outcomes. The failure of physician buy-in is a common barrier to the successful deployment of quality improvement at the provider level.

Table 65.2 summarizes some of the other barriers. It is easy to become discouraged about quality improvement because it does not always work on the first try. In a differential diagnosis of a medical problem, sometimes, many tests with negative results are performed before a positive test result ultimately identifies the nature of the problem. The same is true for quality improvement. Physicians, in particular the medical director of the dialysis facility, must have the patience to champion the quality improvement approach through several unsuccessful cycles until its inevitable success converts the skeptics and is integrated into the facility's culture.

Improvement of physician buy-in to quality improvement can be achieved by giving physicians their own individual data (they are scientists and they love data), by giving physicians comparative data (they are competitive and love to "win"), and by inducing physicians to attend quality improvement meetings by providing refreshments (physicians are busy and most likely to attend meetings if they are concurrent with a meal). The medical director of a dialysis facility should provide leadership for staff physicians by identifying their individual interests and recruiting them as champions of specific quality improvement projects. The medical director is also in the best position to provide liaison among a dialysis facility's governing body, management staff, and medical staff, providing advocacy leadership for the quality agenda and access to the evidence-based literature that may provide a template for process improvement.

The design and implementation of a quality improvement project are relatively straightforward. The leadership of the facility must first make a commitment to adopting a quality improvement culture and providing the data, personnel, and educational resources necessary to its implementation. This could be a clinical outcome such as anemia management, a patient satisfaction issue such as waiting time to begin dialysis, an internal cost-effectiveness issue such as dialyzer selection, or a regulatory issue such as hepatitis testing. Next, an interdisciplinary team with interest and expertise in the project is constituted. Any literature regarding the issue should be gathered and shared among team members. The team should ascertain whether standards for this issue already exist and whether they can be used as a template for process improvement.

The next step is to determine the scope of the data collection activity, including the sources of data, data collection tools, logistics of data collection, and methods of data analysis. The data are then managed to analyze the processes involved and to identify sources of variation. After the analysis of the process has been completed, causes of process variation are identified, and an intervention opportunity is selected. An improvement trial is designed and implemented, and follow-up data are collected and analyzed to determine whether the process change resulted in decreased variation and improved outcomes. Ultimately, the results of the project are reported back to team members, and if the intervention was successful, process change is implemented on a wider scale with continued cycles of follow-up for validation.

It is essential that there be no assignment of blame throughout this quality improvement process. When a problem is identified, it should be determined how the system failed the individual rather than how the individual failed the system. Improvements to the system almost invariably lead to improvements in individual performance, and the "ownership" of the process by those responsible for implementing the process improves consistency, employee morale, and employee retention. The key features of quality improvement in health care are summarized in Table 65.3.

TABLE 65.2 Barriers to Quality Improvement

- Management does not allocate sufficient resources for data infrastructure, employee training, and protected staff time
- Management behavior is not consistent and sends mixed message to employees
- Management fear of employee empowerment
- Lack of physician buy-in
- Failure to identify and train effective team leaders
- Failure to identify a "champion" for a specific project
- Discouragement or impatience regarding an unsuccessful project
- Assignment of blame

TABLE 65.3 Key Features of Health Care Quality

Methods

- Internal and external customer driven
- Management by fact
- Respect for people
- Teamwork
- Disciplined problem-solving process

Results

- *Appropriateness:* Balancing benefit and risk
- *Effectiveness:* Ability of an intervention to achieve the desired outcome in the population
- *Efficiency:* Ability to provide effective care at the lowest possible cost
- *Safety:* Minimizing the adverse effects of interventions
- *Consistency:* Minimize the variability of process and outcome
- *Patient satisfaction:* Ability to meet or exceed expectations

Patient Safety

In 2000, the IOM published its landmark report *To Err Is Human: Building a Safer Health System*, which noted that between 44,000 and 98,000 patients in the United States die each year as a result of medical errors. This makes medical errors the eighth leading cause of death and results in additional national costs of $17 billion to $29 billion, of which health care costs represent more than half. In addition to economic costs, morbidity, and mortality, medical errors result in a loss of trust by patients in the health care system, loss of morale among health care professionals, loss of worker productivity by employers, and reduced school attendance by children.

The authors note that the decentralized and fragmented nature of the health care delivery system contributes to unsafe conditions for patients, yet licensing and accreditation processes have focused limited attention on the issue. Health care organizations and providers have not focused on patient safety because of issues regarding liability risk exposure when efforts to uncover and learn from errors are successful. Medical errors can be of omission or commission. The types of medical errors are summarized in Table 65.4.

TABLE 65.4 Types of Medical Errors

Diagnostic

- Error or delay in diagnosis
- Failure to use indicated tests
- Use of outmoded tests
- Failure to act on results of tests

Therapeutic

- Error in performance of an operation, procedure, or test
- Error in administering a treatment
- Error in the dose or method of using a drug
- Use of outmoded therapy
- Avoidable delay in treatment or in responding to an abnormal test result
- Inappropriate (not indicated) treatment

Preventive

- Failure to provide prophylactic treatment
- Inadequate monitoring or follow-up of treatment

Other

- Failure of communication
- Equipment failure
- Other system failure

Adapted from Leape L, Brennan AG, Troyen A, et al. Preventing medical injury. *Qual Rev Bull.* 1993;19:144.

The IOM report noted that health care services represent a complex and technological industry prone to accidents, especially because many of its components are not well integrated. Nonetheless, much can be done to make systems more reliable and safer because the failure of large systems is due to multiple faults that occur together. One of the greatest contributions to accidents in any industry (including health care) is human error. Humans commit errors for a variety of known and complicated reasons, but most human errors result from system failures. Redesigning the system to prevent human errors is more productive than assigning blame.

Latent errors are more insidious because they are difficult for people working in the system to identify. They may be hidden in computers or layers of management, and people become accustomed to working around the problem. Latent errors can and should be identified long before an active error. These errors pose the greatest threat to safety in a complex system because they lead to operator errors. Current error reporting and response systems tend to focus on active errors but discovering and fixing latent errors and decreasing their duration are more likely to build safer systems because these will prevent active errors before they occur. The IOM report made a number of recommendations to federal agencies and health care providers to improve patient safety.

After the release of the IOM report on patient safety, the Renal Physicians Association, Forum of ESKD Networks, and National Patient Safety Foundation cosponsored a consensus conference of stakeholders in ESKD to establish a patient safety agenda for the ESKD community. Representatives from the large dialysis chains were surveyed to determine which safety issues were of greatest concern at their facilities. These are summarized in Table 65.5. This collaborative effort led to the articulation of 47 action options to improve ESKD patient safety, many of which parallel those of the IOM in the *To Err Is Human* report.

At the individual provider level, efforts will be required to raise awareness about the magnitude of the patient safety issue and the need for change—along with a change in the culture of the provider to a blameless one in which staff regularly report "near misses" without fear of retribution. Systems must be implemented to track errors and adverse events such that patterns can be identified and systems can be improved. Because medical errors occur at the operator level, it is essential that a dialysis unit's staff be trained in the safety sciences and that errors and adverse events are viewed as opportunities for prevention rather than as evidence of individual failure.

Patient safety officers should be designated to stay current with the patient safety literature, which is rapidly expanding so that proven safety practices can be implemented in the facility without delay. As with quality improvement, the key to success in improving patient safety is the cultural change at the organizational level to promote a blameless environment. Health care providers must receive education in the safety sciences, particularly with regard to the importance of error detection and reporting. In addition, a data

TABLE 65.5 Top Dialysis Patient Safety Issues

Patient falls

Medication errors, including:

- Deviation from prescription
- Allergic or other adverse reaction
- Omissions

Access-related events, including:

- Clots
- Infiltrates
- Difficult cannulation
- Poor blood flow

Dialysis errors, including:

- Incorrect dialyzer
- Incorrect blood line
- Incorrect dialysate
- Dialyzer or dialysis equipment–related sepsis

Excessive blood loss, including:

- Separation of blood lines
- Improper hookup
- Prolonged bleeding from needle sites

Adapted from Forum of End Stage Renal Disease Networks, National Patient Safety Foundation, Renal Physicians Association. *National ESRD Safety Initiative: Phase II Report*. December 2001.

collection and reporting infrastructure must be developed to track and eliminate latent errors and near misses before they become active errors and adverse events.

The tensions between the tort system and patient safety demand that the adversarial dispute resolution paradigm in health care be reexamined. Although it is possible that appeals to physicians' ethical commitments to patient welfare and the demonstrated successes of industry-based models of systemic quality improvement may gradually yield to the buy-in to safety initiatives, the success of this approach is doubtful because the conflicts between the tort system and error reduction programs are fundamental and severe. In addition, physicians' concerns about being sued and losing their liability insurance have escalated considerably in recent years. A tort reform strategy may allay some of these concerns by health care providers, but even though it reduces economic exposure, tort reform does not create a more efficient system.

In a no-fault system, an injured patient would only have to demonstrate that a disability was caused by medical management as opposed to the disease process. There would be no need to prove negligence. Such an approach would be better aligned with the blameless philosophy of patient safety and quality improvement, which emphasizes evidence-based analysis of systems of care. A no-fault approach to patient injury would also align incentives for risk reduction, especially if hospitals and their medical staff are insured by the same entity and all efforts to prevent medical errors are undertaken jointly. Blame and economic punishment for errors made by well-intentioned people working in the health care system drive the problem of patient safety underground and alienate people who are best placed to prevent such problems from recurring.

On the other hand, failure to assign blame when it is due is also undesirable because it erodes trust in the medical profession. Although it is important to meet society's needs to pursue legal justice when appropriate, this should not be a prerequisite for compensation as the current tort system requires. Ultimately, for patient safety efforts to succeed, patients, health care providers, and the legal system must understand the distinction between blame-worthy behavior and the inevitable human errors that result from the systemic factors that underlie most failures in complex systems.

Accountability

Even if an ideal blameless culture for patient safety and quality improvement were achieved, there must be accountability. There is a hierarchy of accountability within each dialysis unit organization, between chain facilities and their corporate parent, and among dialysis providers (including nephrologists), payers, regulators, and patients. Because primarily Medicare funds are used to pay for ESKD services in the United States and these funds are appropriated by Congress, Congress holds the Centers for Medicare and Medicaid Services (CMS) accountable for ensuring that the dialysis services purchased with these funds are of high quality.

The mortality rate for ESKD patients in the United States has consistently been higher than that in Europe, Japan, and Australia, and although some argue that this is caused by differences in case mix, data from the U.S. Renal Data System (USRDS) and the Dialysis Outcomes and Practical Patterns Study (DOPPS) suggest that this is not entirely the case. The progressive consolidation of dialysis interests in the United States, dominated by the for-profit dialysis chains, has raised concerns reported in the public press that quality of care has been compromised to maximize stockholder returns, although the data supporting these concerns have been criticized because of unaccounted for confounding factors.

The most recent version of the CfC for ESKD facilities, released in 2008, is a 116-page document that specifies the minimum standards of operation, including governance, patient safety, and patient care, with an emphasis on the use of a formalized quality assessment and performance improvement (QAPI) program by the provider. Adherence to the CfC is monitored by surveyors from individual state Departments of Health, which contract with CMS to

perform onsite surveys of dialysis facilities on an average of every 3 years but more often if triggered by patient grievances or other quality or safety concerns. The state surveyors use as their template the "Interpretive Guidance" of the CfC, a 304-page document also released in 2008, which includes hundreds of "V tags." These V-tags are specific "must" criteria, and if the facility fails to satisfy all of these criteria, it is required to develop a corrective action plan and undergo a resurvey to ensure that the deficiencies have been corrected. Because the CfC and Interpretive Guidance went 32 years between revisions, the Interpretive Guidance has a "Measures Assessment Tool" (MAT) that can be updated more frequently in response to changes in evidence or standards of care. The patient-level indicators in the current MAT are summarized in Table 65.6. It is expected by the state surveyors that dialysis providers will devote a substantial portion of their QAPI activities to the indicators in the MAT, and the surveyors will seek written evidence to that effect.

Research has shown that variation in patient outcomes such as dialysis adequacy is largely attributable to factors at the facility (e.g., its policies governing patient care, associated practice patterns, and attention to individual patient outcomes as opposed to patient-specific causes). Facility-specific data are compiled each year by the Kidney Epidemiology and Cost Center (KECC) at the University of Michigan for every dialysis facility under contract with CMS. The facility-specific profiles are sent to the respective ESKD Networks for distribution to individual facilities and to state surveyor agencies, and some of the data are posted in a "consumer-friendly" form on Medicare's Dialysis Facility Compare (DFC) website (medicare.gov/dialysisfacilitycompare/).

The KECC facility-specific profiles provide standardized mortality (SMR), hospitalization (SHR), readmission (SRR), and transfusion (STR) ratios that use a similar methodology, adding up patient deaths, hospitalizations, readmissions, and transfusions, respectively, for each of the patients in the cohort (corrected for days at risk) and then dividing it by the expected number of events based on patient-specific factors, including demographics, cause of ESKD, and comorbidities. The KECC profile also includes data on transplant wait listing, influenza vaccination rates,

TABLE 65.6 Patient-Level Indicators in the Measures Assessment Tool

Dose of dialysis
- HD duration (>3 hours if three treatments/week and RKF <2 mL/min)
- HD Kt/V (>1.2 adult)
- PD weekly Kt/V (>1.7 adult, >1.8 pediatric)

Nutrition
- Albumin (>4.0 g/dL)
- Body weight
- nPCR measured monthly in pediatric patients

Anemia
- Hemoglobin level (>10 g/dL not on ESA; 10–12 g/dL on ESA)
- Monitor iron stores routinely (ferritin >200 ng/mL HD, >100 ng/mL PD; TSAT >20%)

Mineral and Bone Metabolism
- Calcium monitor monthly (<10 mg/dL)
- Phosphorus monitor monthly (3.5–5.5 mg/dL)
- Parathyroid hormone monitor q3months

Medical injury and errors reporting

Infection control
- Trends
- Immunizations

Vascular access
- Arteriovenous fistulas (prevalent >65%)
- Catheters (<10% >90 days)
- Thrombosis
- Infections
- Patency

Patient satisfaction and grievances
- In-Center Hemodialysis Consumer Assessment of Healthcare Providers and Systems
- Grievances

Health outcomes
- Kidney Disease Quality of Life survey
- Patient survival

Patient education and rehabilitation
- Participation in care
- Preferred modality and setting
- Suitability for transplant referral
- Family and other support systems
- Referral to vocational and physical rehabilitation

ESA, Erythropoiesis stimulating agent; *HD*, hemodialysis; *nPCR*, normalized protein catabolic rate; *PD*, peritoneal dialysis; *RKF*, residual kidney function; *TSAT*, transferrin saturation.

anemia management, dialysis adequacy, vascular access, and mineral metabolism (serum calcium and phosphorus). The SMR, SHR, SRR, STR, adequacy, vascular access, and hypercalcemia data are used to calculate a 1- to 5-star rating for each dialysis facility on the DFC website. Initially, a 1-star rating was given to the bottom 10% of facilities, a 2-star rating to the next 20% of facilities, a 3-star rating to the middle 40% of facilities, a 4-star rating to the next 20% of facilities, and a 5-star rating to the top 10% of facilities. These percentages have changed to a small degree from year to year, with a shift toward a greater percentage of facilities being awarded more stars. A summary of the measures used on the DFC website is provided in Table 65.7. In addition, a separate 1- to 5-star rating is given to each facility on the DFC website based on that facility's patient satisfaction survey performance with the ICH CAHPS (In-Center Hemodialysis Consumer Assessment of Healthcare Providers and Systems) instrument.

In 2012, as part of the bundled payment system for chronic dialysis that began in 2011, CMS initiated a quality incentive program (QIP), which was mandated by legislation in 2008. The legislation provides for withholding up to 2% of a dialysis facility's Medicare payments for a calendar year based on its performance with regard to anemia management, patient satisfaction, and, to the extent feasible, iron management, bone and mineral metabolism, and vascular access. The legislation also requires that such measures be endorsed by the entity under contract for endorsement of clinical performance measures (currently the National Quality Forum [NQF]) or by a consensus organization identified by the Secretary of Health and Human Services. As the data infrastructure for the collection of such measures has evolved from Medicare claims (which included only hemoglobin, urea reduction ratio [URR], and vascular access type) to a web-based network that allows for batch data transmission in real time (CROWNWeb) and more performance measures have been endorsed by NQF, the number of measures included in the QIP has increased from 3 in the payment year 2012 to 14 in the payment year 2024. The QIP measures are classified as clinical care, patient and family engagement, care coordination, and safety. The dialysis facility is given a performance score and an improvement score for each measure based on national norms and awarded the better of the two. The scores for the individual measures are weighted, and a total performance score (TPS) is scaled from 0 to 100 points. For the payment year 2024, which is based on performance in 2022 compared with national norms in 2021, a TPS below 60 or so will lead to a payment reduction, with lower scores leading to greater payment reduction up to 2%. The QIP measures for the payment year 2024 are listed in Table 65.8.

The use of the same data for internal quality improvement activities, external quality oversight, and consumer choice raises several concerns. Traditionally, quality data shared between a health care provider and its respective peer-review organization (or specifically between a dialysis

TABLE 65.7 Measures Reported on the Dialysis Facility Compare Website

- Adequacy of hemodialysis
- Adequacy of peritoneal dialysis
- Arteriovenous fistula prevalence
- Central venous catheter prevalence >90 days
- Hypercalcemia ≥3 months
- Standardized mortality ratio
- Standardized hospitalization ratio
- Standardized readmission ratio
- Standardized transfusion ratio
- Standardized bloodstream infection ratio
- Measurement of nPCR (pediatrics only)
- Transplant waitlist within 1 year of dialysis initiation
- Percentage of patients waitlisted for transplant

nPCR, Normalized protein catabolic rate.

TABLE 65.8 Quality Incentive Program Measures for Payment Year 2024

Clinical Care

- Comprehensive Kt/V dialysis adequacy (includes HD and PD, adult and pediatric)
- Prevalent arteriovenous fistulas
- Prevalent central venous catheters >90 days
- Serum calcium >10.2 mg/dL >3 months
- Standardized transfusion ratio
- Ultrafiltration rate

Care Coordination

- Standardized readmission ratio
- Standardized hospitalization ratio
- Percentage of patients waitlisted for transplant
- Depression screening and follow-up

Patient and Family Engagement

- ICH CAHPS

Safety

- NHSN BSI Measure Topic (infection rate, dialysis event reporting)
- Medication reconciliation

BSI, Bloodstream infection; *HD*, hemodialysis; *ICH CAHPS*, In-Center Hemodialysis Consumer Assessment of Healthcare Providers and Systems; *NHSN*, National Health Safety Network; *PD*, peritoneal dialysis.

facility and its ESKD Network) have been confidential and nondiscoverable so that there is the highest probability that the data will be valid and free of "gaming." Such data can be used to drive internal quality improvement processes at the facility level and allow the respective ESKD Network to target the outlier facilities for confidential and collegial quality improvement intervention activities. As soon as quality data become public (through their release to Medicare state survey and certification agencies, to the DFC website, or other patient-accessible media), there is inevitably a temptation for "gaming" that can undermine the effective use of these same data for internal quality improvement activities.

Another major concern regarding the public release of performance data is that of "cherry picking" of the most compliant and healthiest patients to make a facility's performance measure profile appear more favorable, masking process deficiencies and undermining the quality improvement process. Although most of the community recognizes the need for public accountability by health care providers, there is considerable evidence that patients do not use these data consistently to make choices among health care providers and health care plans. Nonetheless, the public reporting of quality data has sensitized health care providers to their opportunities for process and outcome improvements and, in that sense, has improved the overall quality of health care delivery.

It has been recommended by physician organizations that payment for performance systems start with process measures because these are the most actionable by providers. Outcome measures are used to capture the effect of an intervention on health status or patients' perceptions of care. Although outcome data are often much easier to capture (through a system such as CROWNWeb) than process data, analysis of outcome data and use of outcome data as performance measures require much more statistical sophistication (e.g., case-mix adjustment) than process data.

The kidney care community supports the continued development and application of validated clinical performance measures derived from evidence-based clinical practice guidelines. Nonetheless, many providers fear the advent of "cookbook" medicine in which the training and experience of the practitioner are devalued. Evidence-based clinical practice guidelines, which are designed as clinical decision-making tools, have a misguided tendency to evolve into standards of care. Quality oversight activities then become inappropriately oppressive and cross the line to become the practice of medicine by the regulator.

This is a scenario that ESKD payers, providers, and the patient community must avoid at all costs because it stifles the innovation that leads to quality improvement, returns to the outlier focus of quality assurance, and may ultimately limit access to care as providers begin to cherry-pick patients to avoid the perception of underperformance. The development of a national data infrastructure to allow for provider-specific data collection and provider-specific profiling to drive internal quality improvement activities holds great promise for process and outcome improvement. However, the use of these same data for public accountability carries many concerns that must be addressed because it may undermine the success of the quality improvement partnership between ESKD Networks and dialysis providers. A system of public accountability implemented by CMS must include case-mix adjustment strategies to minimize patient selection bias and encourage facilities to accept high-risk patients without fear that their adverse outcomes may negatively impact their public facility profiles.

Medical Director Responsibilities

The responsibilities of the medical director of a dialysis facility are clearly specified in CfC §494.150 and constitute V-tags 725 to 733 in the interpretive guidance. However, because a medical director's responsibilities encompass all policies and procedures related to patient care, failure of the medical director to be knowledgeable and actively involved in the clinical operation of the dialysis facility may lead to V-tag deficiencies in many domains, particularly safety, staffing, education, adverse events, care planning, QAPI, modality selection, infection control, water quality, and admission and discharge policies. The broad responsibilities of the medical director are summarized in Table 65.9.

The CfC requires that every facility develop, implement, maintain, and evaluate an effective data-driven QAPI program with participation by key members of the facility staff and led by the medical director. Such staff members should include the nurse manager or facility administrator, dietitian, social worker, and other stakeholders in the processes being addressed. The QAPI is designed to achieve measurable improvements in health outcomes and reduction in medical errors by using measures that are tracked over time. QAPI activities are prioritized based on the prevalence and severity of problems and their impact on clinical outcomes and patient safety. The QAPI team is responsible for educating facility staff in QAPI objectives, communicating

TABLE 65.9 Medical Director Responsibilities

- Leading the quality improvement team
- Facility staff training and education
- Infection control
- Water quality
- Dialyzer reuse
- Ensuring patients' rights
- Reviewing adverse events and outcomes
- Developing, reviewing, and implementing patient care policies and procedures
- Reviewing and approving involuntary patient discharges
- Reviewing clinical performance measure data

with the governing body and evaluating the effectiveness of the QAPI program. State surveyors focus on the data and records of QAPI activities, review improvements, and interview staff. The QAPI program will be deemed inadequate by the state surveyor if the facility has failed to recognize and prioritize problems or has failed to develop and follow a written plan for correction.

The medical director is responsible for ensuring that each patient's primary nephrologist participates in the interdisciplinary care team (IDT) care planning for each patient. The IDT must consist of at least the patient or designee, a registered nurse, the physician treating the patient, a social worker, and a dietitian. The IDT must provide each patient with an individualized and comprehensive assessment of their needs and develop each patient's treatment plan and expectations of care. If the patient's nephrologist is not fulfilling their obligations regarding IDT care planning, there must be evidence that the medical director is aware of the situation and has developed a corrective action plan with the nephrologist.

The medical director is responsible for water quality in the dialysis facility and is expected to be familiar with components of the water treatment system. The medical director should have basic knowledge of maintenance procedures and triggers for intervention, should review and sign off on monthly testing of the water system and dialysis machines, and should lead QAPI activities regarding water quality as appropriate.

The medical director is chief infection control officer of the facility and must be familiar with its infection control program. The medical director must review all infection control reports, document action to address problems, and is ultimately responsible for reporting adverse event clusters to public health authorities. Infection control issues in the CfC with which the medical director should be knowledgeable are listed in Table 65.10.

TABLE 65.10 Infection Control Responsibilities of the Medical Director

- Isolation of hepatitis B–positive patients
- Contact precautions for skin wounds and fecal incontinence
- Strict hand hygiene
- Environmental cleaning and disinfection of dialysis stations
- One-way flow of supplies and medications
- Routine serologic testing of hepatitis B and C
- Immunization for hepatitis B, influenza, and pneumococcus
- Infection control training of staff and patients
- Infection surveillance (e.g., catheter-related bacteremia)

Other medical director responsibilities include approving the training program for patient care dialysis technicians; developing, reviewing, or approving patient care policies and procedures; signing off on all involuntary discharges and transfers; and incorporating reports regarding quality metrics from external agencies into the QAPI. Such reports include the dialysis facility report from KECC, QIP data, DFC data, ESKD Network data, patient quality of life and experience of care data, and national comparatives from the USRDS and the Dialysis Outcomes and Practice Patterns Study.

In summary, the CfC makes the medical director the "captain of the ship" for quality in the dialysis facility with responsibilities that are far reaching and time consuming and that may require political and administrative skills that are not intuitive. Nonetheless, Medicare has acknowledged that the nephrologist is best suited for the job, which has become increasingly complex as the emphasis on quality and safety has evolved to affect not only facility surveys and certification but also payment and public reporting. In recognition of the importance of this role, many professional societies have developed medical director curricula at their national meetings, and the *Clinical Journal of the American Society of Nephrology* has published a series of articles addressing the responsibilities and challenges facing medical directors.

Recommended Reading

Corrigan JM, Eden J, Smith BM, eds. *for the Institute of Medicine. Leadership by Example: Coordinating Government Roles in Improving Health Care Quality.* Washington, DC: The National Academies Press; 2003.

This book by the IOM puts the responsibility for health care reform squarely on the federal government and proposes a national quality enhancement strategy.

Gupta N, Wish JB. Do current quality measures truly reflect the quality of dialysis? *Semin Dial.* 2018;31:406–414.

A critical appraisal of the dialysis quality metrics used for payment and public reporting.

Hingwala J, Tangri N, Rigatto C, et al. Improving the quality and efficiency of conventional in-center dialysis. *Semin Dial.* 2015;28:169–175.

The application of contemporary quality improvement and operations research concepts to dialysis, including scorecards, process mapping techniques, and LEAN principles.

Institute of Medicine. *Crossing the Quality Chasm: A New Health System for the 21st Century.* Washington, DC: National Academy Press; 2001.

This landmark book from the IOM calls for a sweeping redesign of the American health care system to improve quality and decrease disparities in processes and outcomes.

Kohn LT, Corrigan JM, Donaldson MS, eds. *for the Institute of Medicine. To Err Is Human: Building a Safer Health System.* Washington, DC: National Academy Press; 2000.

This landmark book from the IOM documents the staggering incidence of medical errors and their consequences and recommends that fundamental system changes be made to ensure patient safety.

Leape LL, Berwick DM. Five years after To Err is Human: what have we learned? *JAMA.* 2005;293:2384–2390.

A follow-up to the patient safety manifesto by the IOM that includes accomplishments, barriers, and a roadmap for the future.

Maddux FW, Nissenson AR. The evolving role of the medical director of a dialysis facility. *Clin J Am Soc Nephrol.* 2015;10:326–330.

The first in a series of nine articles in the Clinical Journal of the American Society of Nephrology that comprehensively cover the major responsibilities of the medical director, including quality oversight, safety, infection control, water quality, challenging patients, and legal issues.

Saha S, Wish JB. Leading the dialysis unit: role of the medical director. *Adv Chronic Kidney Dis.* 2018;25:499–504.

A review of the application of leadership principles to becoming an effective dialysis unit medical director.

The National Forum of ESRD Networks. Medical Director Toolkit, 2012. Available at: https://media.esrdnetworks.org/documents/Outpatient_Medical_Director_Toolkit_2021_1118_combined.pdf.

A comprehensive compendium of medical director resources including quality improvement tools, templates, and self-assessment instruments.

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Application of Telemedicine to Kidney Failure Patients

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Telemedicine in Kidney Failure: Overview of the Opportunity and Issues

Telemedicine is rapidly becoming a consistent part of health care delivery. While the term "telemedicine" includes any delivery or monitoring of care remotely, including telephonic care, the contemporary definition includes the use of video and the remote delivery of computer data. Telemedicine has historically seen a relatively low adoption rate, largely due to concerns around quality of care delivered without a live interaction and reimbursement issues. As technology and consumer expectations around how their care will be delivered have evolved, there has been a slow but sustained increase in use in many avenues of nephrology care, including in the care of kidney failure patients.

The 2020 COVID-19 pandemic accelerated many nephrologists' adoption of telehealth for hospital, office, and kidney failure care, for patients treated with both in-center and home modalities. Health systems of all sizes quickly enabled telehealth programs in response to the pandemic, and regulatory waivers provided additional flexibility around the use of telehealth. Despite this rapid expansion of the use of telehealth with dialysis patients, many questions remain unanswered—including understanding the clinical impact and the best practices for implementing a telehealth program.

In this chapter, we will focus on telehealth defined as the ability to remotely monitor and interact with patients undergoing dialysis with the use of audio and video two-way communication. Physicians or other care providers may be in an off-site location, such as their clinic office. Patients may be in free-standing dialysis clinics, at home, or receiving kidney replacement therapy in the hospital.

The general framework required for telehealth parallels the way that patients in intensive care units (ICUs) are monitored by a central physician through eICU systems. Such systems have been described as follows: "tele-ICU delivers technology-enabled care from a remote command center. At its simplest, mobile platforms provide on-demand, two-way, audiovisual (AV) communication between ICUs and the tele-ICU center. Typical infrastructure is more complex and involves a tiered system of fixed AV communication, access to Electronic Medical Records (EMRs), telemetry, and imaging systems for data retrieval and documentation, plus risk stratification and decision support."

Telemedicine/Virtual Intensive Care Unit: Where Are We and Where Are We Going?

The ability to monitor outcomes and communicate on demand has proven effective and has been associated with increased best-practice adherence, improved patient outcomes, and positive experiences for patients and caregivers in the hospital setting. Thus, the use of telemedicine in the ICU informs the use of similar programs in outpatient settings such as dialysis.[1]

In some parts of the world, a nephrologist is required to be in the facility when dialysis treatments are being delivered. This regulatory requirement is historical and may reflect previous issues requiring a physical presence, such as the use of acetate-based dialysate. This regulatory requirement does not exist in other regions, such as the United States. However, the global COVID-19 pandemic has necessitated a rapid reassessment of the risks and benefits of direct nephrologist supervision versus the need to cohort and sometimes quarantine patients and staff based on COVID-19 status. As a result, the use and evolution of telemedicine have increased dramatically in some countries.[2]

This rapid increase in telemedicine use may help solve the increasingly pressing issue of the declining number of nephrologists worldwide. Telehealth may allow the nephrology community to scale more effectively to provide high-quality dialysis care to a growing population in a wider variety of geographically separate care venues. This is especially true in rural areas where requiring a nephrologist to be physically, as opposed to virtually, present may be a

rate-limiting factor in terms of providing access to dialysis. Use of telemedicine may be even more important for the increasing number of patients who dialyze at home.

From a more consumer-oriented perspective, telehealth appears to be a reflection of a broader shift in philosophy around care to become more patient directed. The authors have observed that home-based dialysis modalities have been on the rise, in light of the recent Executive Order in the United States, as well as an increased focus on self-sufficiency among patient populations in managing and directing their own care. Nephrologists must still monitor these patients, and telehealth, remote patient monitoring, and other technology solutions help provide the bridge and connection point between patients and providers in this new paradigm.

The Health Care System in the United States Presents Particular Challenges

According to the Center for Connected Health Policy, all 50 U.S. states and the District of Columbia now reimburse for some type of live video telehealth services.[3] That said, reimbursement for remote patient monitoring, frequently used in the kidney care space to monitor patients using peritoneal dialysis (PD) at home, varies state by state.

Given the increased use of telemedicine for kidney care in the United States both before (mainly home dialysis) and during the pandemic (all modalities), examining the payment challenges by payor type and by modality provides a useful framework for anyone in the dialysis and nephrology space considering implementing a telehealth program.

- *Physician reimbursement:*
  - *Medicare*: Reimbursement for remote dialysis rounding is limited to originating sites and must either be outside the metropolitan statistical area or in an area with a health professional shortage. The vast majority of dialysis patients have traditional Medicare; therefore, CMS has tremendous influence on the reimbursement of telehealth.
  - *Medicaid*: Reimbursement for telemedicine varies by state. Trends indicate reimbursement for telemedicine is on the rise.
  - *Private insurance*: There are no consistent standards governing private payors; however, states continue to pass parity laws requiring telemedicine reimbursement.
- *ESRD Conditions for Coverage (CfCs)*: Medicare CfCs certify the facility as qualifying for Medicare payment.
- *Health Insurance Portability and Accountability Act of 1996 (HIPAA)*: Absent pandemic-related waivers around originating site and telehealth platform choice, best practice is for programs to ensure that HIPAA guidelines are followed at all times, including technology hardware and software selection, as well as in-center patient care.
- *Licensure*: Physicians are required to be licensed in the state where the patient is located, not where the physician is located. However, there are coalitions of states that are offering various forms of reciprocity with regard to interstate telehealth licensing. Given the complexity, clinicians are advised to keep in touch with state medical societies in both originating and destination location states if care is being rendered across state lines.
- *Malpractice*: According to the *AMA Telehealth Playbook*, the American Medical Association (AMA) recommends the following to minimize potential risk associated with telemedicine:
  - Include the legal and billing team as early in the process as possible to understand federal, state, and payer requirements and regulations.
  - Identify in which states your clinicians need to be licensed as well as in which states they are currently licensed.
  - Research interstate licensure, including the Interstate Licensure Compact.
  - Check with your malpractice insurance carrier to ensure you are covered to provide telehealth services.[4]

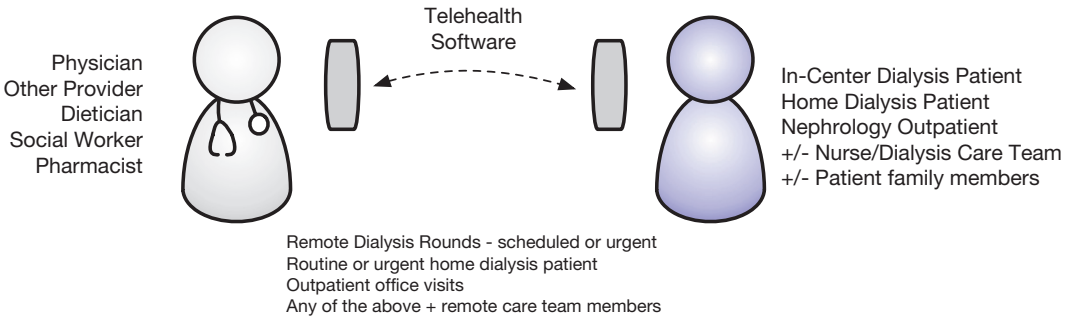
Similar variants of these issues no doubt occur in many countries of the world. However, that is rapidly changing given the evolving technology and pandemic needs.[5]

A Framework for Implementation of a Telehealth Program

As mentioned earlier, there are two specific aspects of telehealth. The first is a variant of traditional telemedicine, which leverages a video visit to facilitate diagnosis and treatment. Here, the essential capability is for a clinician to remotely interact with the patient and/or remote caregiver to allow diagnosis and treatment.

The second aspect focuses on remote patient monitoring, creating a virtual ability for the remote clinician with the same fidelity as if the provider were physically present on site. Achievement of this goal requires access to electronic medical records, telemetrics that provide either real-time streaming or batched submission of data from a dialysis machine or ancillary device, such as a blood pressure cuff or remote stethoscope and some type of virtual presence in the form of audio and video communication. This type of remote patient monitoring will most often be used in the home setting but may also be used with remote care sites and centralized monitoring of in-center facilities.

This framework of both the telehealth encounter and remote patient monitoring requires consideration of the originating and receiving sites. The patient's location is considered the originating site for the telehealth program. The patient is typically located at either a clinic in the case of in-center dialysis or the patient's home in the case of home modality patients. The physician's location is designated as the receiving site. This could be any number of physical locations, including the provider's office, a hospital location, or the physician's home, among others. The originating and receiving sites are the two required



• **Fig. 66.1** Conceptual model of telehealth by modality.

locations in terms of regulatory and billing requirements. However, if other members of the patient's care team join the telehealth encounter for interdisciplinary rounding, their locations are additionally receiving locations. This is described in Fig. 66.1.

Having defined the framework of the telehealth system, we move to define specific use cases or scenarios in which the telehealth program needs to function, as well as the various supports (training, devices, and documentation) required to make the telehealth program effective.

Use Cases

Routine Nonemergent Nephrologist/ Interdisciplinary Rounding

A routine use case involves remote scheduled rounding by a nephrologist, which may also include other members of the care team, such as social workers and dieticians. For the in-center hemodialysis scenario, the nephrologist contacts the dialysis unit at a predetermined frequency or has previously established a block of time for telehealth to conduct rounding on one or more patients who are dialyzing in the unit at that time. If there is a single shared device at the location on which the telehealth encounter is rendered, the care team at the dialysis center originates a telehealth encounter with the physician at the designated time. The remote nephrologist uses a combination of the audio/video feeds, information in the electronic medical record, and in the case where remote patient monitoring is in place, real-time data transmitted from connected cyclers, connected peripherals (scales, blood pressure cuffs, glucometers), and/or other medical devices to conduct rounds. Notes and findings are entered into the EMR.

The telehealth device may be manually moved from patient to patient by the facility staff, adhering to proper infection control procedures. In more robust scenarios, clinics would provide telehealth applications on devices at the patient's chairside or facilitate a "bring your own device" option for telehealth, whereby patients download the telehealth application on their personal smartphone or tablet. The logical flow for such an interaction is detailed in Fig. 66.2.

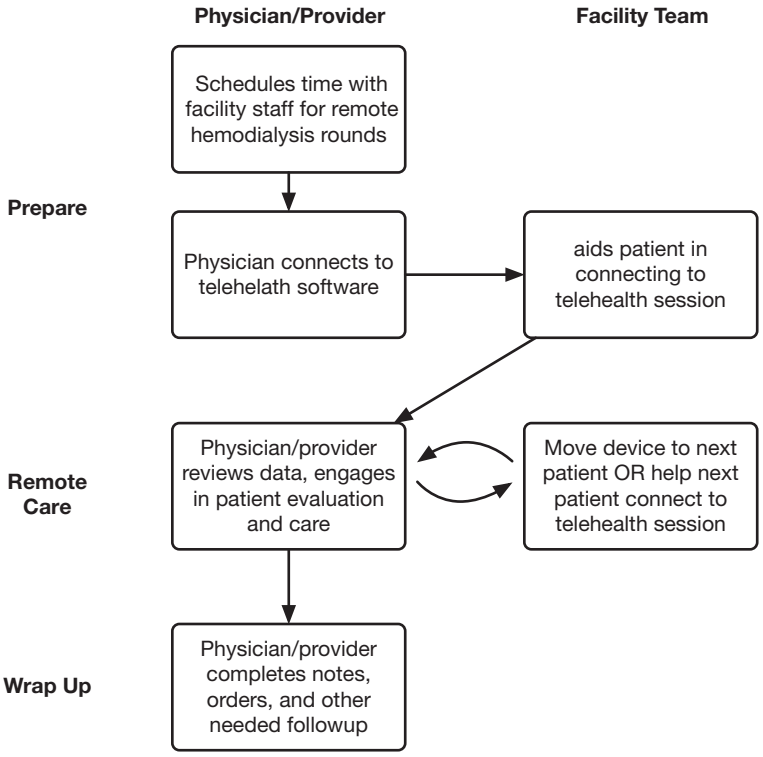
Home and Peritoneal Dialysis: Remote Monitoring

Adaptations of the previous use case can be applied to home hemodialysis and PD. Because these patients have less frequent direct contact with their caregivers today, there may be a significant opportunity for remote monitoring to improve the overall health of patients and ultimately prevent hospitalization episodes or other adverse events.[6] The primary application today is routine remote monitoring of patient vitals and overall health along with periodic bidirectional video and audio visits with nephrologists and/or any member of the care team.[7] Baseline remote monitoring metrics include weight, blood pressure, pulse and heart rhythm, symptomatology, temperature, blood glucose values, and treatment and machine alarm data.

Home dialysis patients tend to be younger than in-center dialysis patients and may be more likely to have access to devices that permit telehealth visits. As capabilities are further developed to use widely available communications devices and technology, the business case for broader adoption becomes more compelling.

Emergent Use Cases

Telemedicine may also play a role in the emergent consultation request, such as the situation in which a remote dialysis unit has an acute issue requiring immediate intervention by a trained nephrologist. Such emergent situations require regional definition but may include scenarios such as acute hypotensive events, dialyzer reactions, seizures, and cardiac arrest. Communications in this scenario may be fundamentally by phone, augmented by access to the patient's electronic records. In a more complex system, real-time telemetric data detailing vital signs and dialysis parameters may be used, supplemented by video connections allowing the remote nephrologist to be virtually present in the dialysis unit and gather the needed information for both diagnosis and treatment. While this may be as simple as an Internet-enabled camera, this communication may be as complex as to involve a remote robot, with the ability to "see" the patient and gather some vital information through the use of



• **Fig. 66.2** Logical diagram of telehealth.

a remote microphone, stethoscope, or other tools. A sample flow for such a situation is detailed here.

- Dialysis clinic nurse and/or internists identifies emergent patient situation
- Call placed to central nephrologist in monitoring station
- Central nephrologist reviews streaming data and/or real-time data at central site
- Central nephrologist makes video connection to nurse/internist at the patient bedside
- Central nephrologist conducts virtual assessment and medical interventions
- Central nephrologist documents in EHR

Other Miscellaneous Use Cases

Other use cases for telehealth include more frequent remote visits for high-risk patients, follow-up on missed rounding due to schedule conflicts, visits to support transitions of care after an unexpected hospital admission, interim medication reviews (including viewing medication and bottles), updating history and physical data in preparation for surgery and educating patients about complex concerns between face-to-face appointments. Due to legal and compliance restrictions, video interactions may be limited to credentialed caregivers.

Integrated Kidney Care (Global Capitation) Use Case

The goal of integrated care is to improve the quality of patient care while simultaneously lowering costs. Telemedicine is a helpful tool in this model, offering efficient care delivery through more frequent and timely access to care managers and providers. Typically, dialysis centers are not credentialed to provide additional services. However, current initiatives such as the ESRD Seamless Care Organization (ESCO) accountable care model allow patients to connect to members of their care team and external specialists via telehealth in pursuit of more integrated care for dialysis patients via the dialysis center. In the future, centers may more pervasively offer patients a wider range of specialty consultations while receiving their treatment. Given the significant comorbidities that exist with dialysis patients coupled with the transportation challenges for many patients, the dialysis center of the future could be an epicenter for comprehensive patient care. Telemedicine could play an important role in delivery of that care.

Telehealth Technology Requirements

Technology evolves so rapidly that "best practice recommendations" are quickly outdated. Nevertheless, telemedicine technology advancements are much more of an opportunity than a concern. Examples of evolving technology include the variety and capacity of broadband connections, new software and hardware technologies, and increased numbers of patients with access to affordable and capable consumer tools.

There are foundational technical infrastructure requirements that are essential for a successful telemedicine program, including secure and sufficient network/broadband

connectivity to support video and audio transmission, as well as the software and devices to facilitate the telehealth encounter. These devices can include a computer with a camera, a tablet, or a smartphone. There are several HIPAA-compliant telehealth software vendors that provide secure software to facilitate video visits and remote patient monitoring.

Relevant Network and Security Requirements

Most basic to a telemedicine practice is a secure broadband Internet connection. The bandwidth and speed of the internet connection will determine the video quality, along with the quantity and speed of data transfer. A basic business broadband connection should be sufficient.

Network connection requirements will vary based on location as well as the number of participants who join the encounter from discrete locations. For example, for a provider in a busy clinic location connecting with patients in a dialysis clinic where other patients and clinicians are using the wireless connection, 1.2 mbDn/1.2 mbUp may be required for a video visit with seamless audio and video without delay. However, for providers connecting with a PD patient in their home without a lot of other network use, 700 kDn/700 kUp may be sufficient bandwidth for a successful telehealth encounter.

With regard to specific security requirements, contemporary standards around the encryption of data in transit are to use TLS or a similar secure protocol when using TCP/IP. For data at rest, encryption of data using AES-256 encryption is advised.

Hardware and Video Requirements for Devices

Hardware/Functionality: When researching full digital/camera carts versus tablets, benefits, and tradeoffs of functionality and cost must be considered. For example, tablets cost significantly less, take up less space, and may be easier to manage in more confined treatment areas at many inpatient centers. Different carts and tablets provide varying flexibility for multifunctionality, including rounding, EMR, telemetric, and video transmission.

As noted earlier, another option is to allow for the deployment of telehealth video visits and remote patient monitoring software to be downloaded to a patient's personal device. This type of solution may be best deployed among patients who possess a high degree of technical proficiency and who prefer to take an active role in their own care.

Video: Ideally, each dialysis station would have a device with a camera with the ability for the nephrologist or data access technician to connect to a specific station. This may be facilitated by the use of a microphone to allow the originating site to communicate with the destination central monitoring or provider location. In less robust scenarios, a telephone connection may be used to provide the clinician with information regarding which patient is at which station at the center.

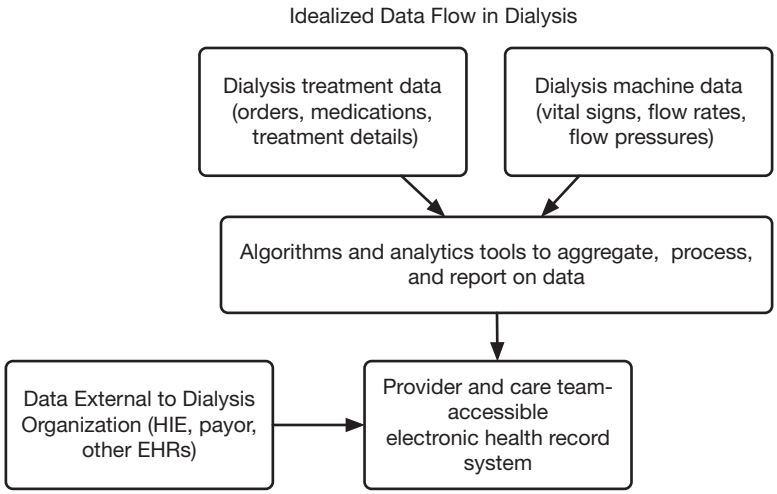
Other: Medical and related devices for remote data capture are rapidly advancing. Consider devices such as digital stethoscopes that connect through the video conferencing software without additional software.

Telehealth requires a clear understanding of how the needed data elements flow from originating sites to remote locations through various systems. In our system, data flows as per the diagram in Fig. 66.3.

Dialysis Machine Data

At present, there is a lack of consistency in the data format that can be streamed from various dialysis machines, necessitating a custom interface for each. This is inefficient and decreases data consistency. Solving this issue as a community is important for large-scale implementation and adoption of telehealth.

A global data model has been defined by the dialysis community (in conjunction with HL7) to define the



• **Fig. 66.3** Draft telehealth workflow. *EHR*, Electronic health record; *HIE*, Health Information Exchange.

TABLE 66.1 Data Elements

Vital Signs Data

Sample data elements include:

1. Treatment duration
2. Pretreatment blood pressure sit
3. Pretreatment blood pressure stand
4. Posttreatment blood pressure sit
5. Posttreatment blood pressure stand
6. Pulse
7. Liters processed
8. Average blood flow rate
9. Dialysate flow rate
10. Volume removed
11. Lowest blood flow rate

minimum data elements for dialysis machine streaming data that will be submitted to an international standards committee for balloting in 2021. Dimensions of this data model include mandatory and optional data fields, unified field names with a crosswalk to each machine type, and the frequency of data transmission. Support for this data model will require adoption by both hardware vendors and software systems to ensure maximum utility. Alarm data are an additional real-time parameter that can be monitored remotely. While reacting to alarms is a local clinic responsibility, it may be beneficial to have the alarms centrally or remotely monitored.

A sample minimum data set for dialysis data streaming may include those shown in Table 66.1.

Nontechnology Telehealth Requirements

Policy and Procedures

Given the complexity of the medical and regulatory parameters that govern the use of telehealth, it is crucial to have a solid set of policies and procedures (P&Ps) to ensure success. Essential P&Ps include a Scope of Service Template, a Quality Review Policy Template, a Physician Credentialing Policy Template, a Chairside Physician Communication Policy Template, and a Complaint Response Policy. Given that regulations around the scope of practice and telemedicine are country (and even state) specific, proper attention to the appropriate regionalization of these P&Ps is critical.

Documentation is another regulatory aspect that requires formalized evaluation and description. Two common models exist. The first is consultative only, with no documentation other than the originating site stating they contacted the central nephrologist. The second is where the remote site documents the encounter in the local or shared EMR. While either may be acceptable, the second is preferable to ensure continuity of care in a patient-centric informatics environment.

Program Management and Implementation

A proper program management framework is critical to program success. Best practices in program management include (but are not limited to):

1. Getting buy-in from nursing and clinic staff early in the process. This can be done by highlighting how telehealth or remote data monitoring can improve access to care and, potentially, clinical outcomes. Moreover, having participating nurses comfortable with the technology and pilots is key to ensuring that nurses are motivated to keep patient adherence high, especially when it comes to patient compliance with remote monitoring data.
2. Actively involved administrative staff. This could include dedicated and detailed support to supervise nurses, ensure adherence, and answer challenges nurses face during rollout, which helps increase the viability and sustainability of the program.
3. Engaged physicians who are excited about testing new technology for patient care, especially if there are reimbursement hurdles.
4. Device strategy. Depending on the scale and scope of the telehealth initiative, it will be important to consider which patient-facing devices will be used to render the telehealth encounter. Will it be a facility-provided tablet or the patient's personal electronic device? If connecting with PD patients at home, will the organization provide a device and/or internet connectivity to support the telehealth encounter?
5. Scheduling. Best practice dictates that the nephrologist works with the dialysis center clinical team to schedule specific blocks for rounding to reduce the impact on the dialysis staff in coordinating with patients and moving any devices around between encounters.
6. Dedicated project manager. It is important to have one dedicated staff member responsible for data collection and liaising with the various organizations involved to ensure the collection of data. The project manager is ideally responsible for collecting and publishing monthly data on specific types of hospitalizations, readmissions, and patient engagement.
7. Tech support. The project manager may need to be supplemented with a tech rep who ensures that remote monitoring patients are installing and using their devices properly.
8. Legal/Compliance. Reviews of the regulatory, HIPAA, credentialing, and other factors are required to mitigate risks incurred with telemedicine.
9. Measurement of success. It is important to measure success to ensure that any investment in telemedicine is worthwhile. Metrics may come from multiple sources, such as:

- Providers (e.g., dialysis center or hospital, physicians)
- Technology partner
- Individuals via feedback

Potential metrics to track include:

- Experience of telemedicine visit via survey or interview (patient, physician, facility)
  - Was video important for the intervention?
- Visit frequency, quality, and length of time
- Nature of visit (e.g., was a hospitalization or missed treatment avoided?)

Training

As with any new endeavor, staff and physician training is essential to the smooth operation of a telemedicine program. At least one member of the remote dialysis unit should be trained in the facile operation of the equipment. Nurses need to be trained on the types of issues that may or may not be amenable to telehealth. Nephrologist training includes training on the technology system as well as training on documentation.

Paper and soft copy instructions and reference materials on use cases, metrics tracking, cleaning and maintenance, and support are helpful resources, as well as clear training and reminders on HIPAA protection, logging out of EMR systems on a tablet that is multiuse, and other risks to regulatory and corporate P&Ps.

Examples of Telehealth in Use Today

There are many examples of telemedicine being used in dialysis clinics today. For example, the DaVita Colombia dialysis clinics are testing a Telehealth setup to allow remote dialysis clinics to be connected and monitored by a centrally located nephrologist. As a result of this new innovative approach, patients can avoid having to travel great distances to receive dialysis. Another example is in Scotland, where a satellite dialysis unit is monitored from a central hospital (http://news.bbc.co.uk/2/hi/uk_news/scotland/highlands_and_islands/8634562.stm). One of the oldest programs for telehealth exists in the northern reaches of Finland, where remote rural units are monitored from a central university hospital using video and other communications media. Teledialysis has also been used for 5 years in a dialysis program in France.[8]

Conclusions

As the number of dialysis patients increases and the number of nephrologists continues to be rate-limiting, telehealth has the potential to allow the nephrologist to continue to care for patients in multiple settings. Additionally, the recent COVID-19 pandemic has significantly increased the use of telehealth with dialysis patients and offers an opportunity to revisit the successes of telehealth with an eye toward capitalizing on these opportunities in the future.

In implementing a telehealth program, it is fundamental to have a clear understanding of the local regulations and the technology and nontechnology requirements. The most common use cases for telehealth can then be mapped against these requirements to ensure that the program is successful. Future efforts to standardize dialysis streaming and other data sets will continue to improve the efficiency and efficacy of telehealth toward the goal of improving the lives of patients with kidney failure.

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SECTION 7

Acute Kidney Injury and Poisonings

67

Continuous Renal Replacement Therapies for Acute Kidney Injury

ETIENNE MACEDO, MD, PhD • RAVINDRA L. MEHTA, MBBS, MD, DM

Acute kidney injury (AKI) is a clinical syndrome characterized by an abrupt decrease in kidney function. It leads to the inability of the kidney to excrete waste products, manage electrolytes, regulate fluid balance, and maintain acid-base status. Based on the Kidney Disease: Improving Global Outcomes (KDIGO) definition, the most recent epidemiological studies estimate that AKI occurs in 21% of hospital admissions, and overall, 11% of patients with AKI will require dialysis. AKI is associated with an increased risk of mortality, reaching greater than 50% in severe AKI and up to 80% when renal replacement therapy (RRT) is required in the ICU. Continuous RRT (CRRT) has been increasingly used, especially in the Intensive Care setting. This chapter reviews the basic techniques of CRRT and its applications, dosing, and outcomes in AKI.

Basic Principles and Operational Characteristics

CRRT is actually an umbrella term for four different continuous modalities: slow continuous ultrafiltration (SCUF), continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF). The type of modality chosen depends on the goal of therapy and experience of the center. Treatment may be used for solute removal, fluid removal, or both. Solute clearance through a dialysis filter occurs by diffusion, convection, or combination, called hemodiafiltration (Tables 67.1–67.3 and Fig. 67.1).

Convective techniques (ultrafiltration [UF] and hemofiltration) rely on solvent drag, whereby dissolved molecules are dragged along with ultrafiltered plasma water across a semipermeable membrane in response to a hydrostatic or osmotic force. The process of forcing fluid against a membrane is called ultrafiltration; the fluid collected after it passes through a membrane is the ultrafiltrate. Depending on the amount of UF, fluid replacement is required to prevent hemodynamic instability associated with fluid removal. Solute removal depends on the size of the pores in the membrane, the size and weight of the molecule, the transmembrane pressure, and the UF rate (UFR; Q_{uf}). Middle- and large-molecular-weight solutes are more effectively cleared by convection. SCUF and CVVH only use convective transport for removal of solutes.

Diffusive techniques (dialysis) rely on a solute concentration gradient between the blood and the dialysate for clearance across a semipermeable membrane. Solute removal depends on the size of the pores in the membrane, the size and weight of the molecule, and the magnitude of the concentration gradient. The gradient is affected by the dialysate, dialysate infusion rate (Q_d), and blood flow rate (Q_b). The dialysate runs countercurrent to the blood and can be customized to promote the diffusion of specific molecules. This is the same technique used in intermittent hemodialysis (IHD), but Q_d is much slower than Q_b, so complete saturation of the dialysate can be reached. Therefore, the Q_d is the rate-limiting factor for solute removal. The smaller the size and weight of the solute and the greater the gradient, the more efficiently solute clearance occurs. CVVHD uses diffusion to remove solutes.

CVVHDF combines both convection and diffusion to clear solutes, utilizing both dialysate and replacement fluids. This modality allows for removal of small- and middle-sized molecules. Solute clearance for this combination technique is equal to the sum of the convective and diffusive clearances. The clearance is the product of a solute's sieving coefficient (SC; ratio of solute concentration in filtrate to solute concentration in plasma) and effluent flow rate (dialysate plus ultrafiltrate). A solute with an SC of 1 means that it can pass freely through a filter; if the SC is 0, then a solute cannot pass through the filter at all.

TABLE 67.1 The Four Principle Modalities Used for Continuous Renal Replacement Therapy

Modality	Urea Clearance (g/day)	Replacement Fluid	Dialysate	Solute Transport	UF Flow (mL/h)	Dialysate Flow (mL/h)
SCUF	1–4	No	No	Convection	100–400	0
CVVH	22–24	Yes	No	Convection	500–4000	0
CVVHD	24–30	No	Yes	Diffusion	0–350	500–4000
CVVHDF	36–38	Yes	Yes	Convection + diffusion	500–4000	500–4000

CVVH, Continuous venovenous hemofiltration; *CVVHD*, continuous venovenous hemodialysis; *CVVHDF*, continuous venovenous hemodiafiltration; *SCUF*, slow continuous ultrafiltration.
From Galvagno SM Jr, Hong CM, Lissauer ME, et al. Practical considerations for the dosing and adjustment of continuous renal replacement therapy in the intensive care unit. *J Crit Care.* 2013;28(6):1019–1026.

TABLE 67.2 Mechanisms of Clearance for Various Solutes and Molecules in Continuous Renal Replacement Therapy

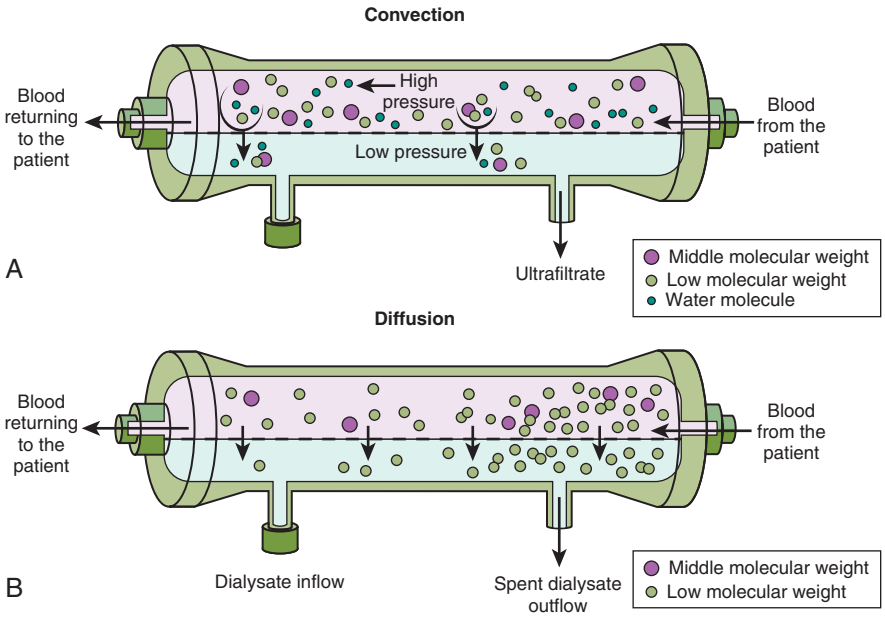
Molecular Size	Small Solutes (< 300 Da)	Middle Molecules (500–50,000 Da)	Low-Molecular-Weight Proteins (5,000–50,000 Da)	Large Proteins (< 50,000 Da)
Substances	Urea, creatinine, amino acids	Myoglobin, B_{12}, vancomycin	Inflammatory mediators	Albumin
Clearance mechanism	Convection/diffusion	Convection	Convection ± absorption	High cut off filtration

From Galvagno SM Jr, Hong CM, Lissauer ME, et al. Practical considerations for the dosing and adjustment of continuous renal replacement therapy in the intensive care unit. *J Crit Care.* 2013;28(6):1019–1026.

TABLE 67.3 Continuous Renal Replacement Therapy Terminology

Term	Definition
Ultrafiltrate (UF)	Fluid collected in bag distal to hemofilter
Dialysate	Fluid instilled into filter countercurrent to flow of blood
Effluent	UF (+ dialysate)(+ replacement fluid)
	(depending on which modality of CRRT is used)
Replacement fluid	Fluid instilled pre- or postfilter to replace UF volume
Sieving coefficient (SC)	Ability of substance to pass through filter
	Ratio of solute concentration in filtrate to solute concentration in plasma
Solvent drag	Free circulating, unbound solute carried with water during UF
Filter permeability/efficacy	Ratio of effluent FUN to BUN < 1, decreased efficacy
Concentration polarization	Accumulation of rejected solutes on the blood compartment side of the ultrafiltration membrane
Q_b	Blood flow rate
Q_d	Dialysate flow rate
Q_r	Replacement flow rate
Q_{uf}	UF rate
Q_{net}	Net fluid removal rate
Q_{bw}	Blood-water flow rate
	$= (1 - \text{Hematocrit}) \times Q_b$

BUN, Blood urea nitrogen; *CRRT*, continuous renal replacement therapy; *FUN*, fluid urea nitrogen; *UF*, ultrafiltration.
Adapted from Galvagno SM Jr, Hong CM, Lissauer ME, et al. Practical considerations for the dosing and adjustment of continuous renal replacement therapy in the intensive care unit. *J Crit Care.* 2013;28(6):1019–1026.



• **Fig. 67.1** (A) Convection occurs when solutes are transported across a semipermeable membrane with plasma water in response to a hydrostatic pressure gradient that is created on the blood side of the hemofilter. Convection enhances the removal of low- and middle-molecular-weight molecules. As shown in panel (B), in diffusion, movement of solute across a semipermeable membrane is driven by a concentration gradient between the blood and the dialysate. Solutes move from the side with the higher concentration of particles to the side with the lower concentration. Diffusion is best for clearing low-molecular-weight solutes, such as urea and creatinine. (From Tolwani A. Continuous renal-replacement therapy for acute kidney injury. *N Engl J Med.* 2012;367(26):2505–2514.)

Technical Issues

Vascular Access

The location and size of the vascular access are important for ensuring successful CRRT. The optimal site for catheter location is determined by the risks of the catheter placement procedure and the possibility of thrombosis, stenosis, and infection. The right internal jugular (IJ) vein is preferred for temporary catheters because it allows for a more direct route to the superior vena cava as compared to the left jugular vein, which can cause reduced blood flow in patients with head movements. Double lumen uncuffed central venous catheters or tunneled cuffed catheters can be used. Cuffed catheters are preferred in patients expected to require prolonged RRT duration, more than 7 days. They provide significantly better catheter survival and fewer infectious and thrombotic complications. On the other hand, they require more time for insertion and have an increased risk of hematoma formation. CRRT circuit survival is improved when a larger bore catheter is used because it allows for higher Q_b rates. The diameter of the catheter has more influence on flow resistance than the length of the catheter. For adults, catheter diameters range from 11 to 14 Fr. See Table 67.4 for suggested catheter sizes in pediatric patients. A longer catheter does allow placement into a larger vessel, such as the femoral vein. A single-center randomized trial found that placement of a longer (20–24 cm) soft silicone short-term catheter into the right atrium from the IJ or subclavian vein improved dialyzer life span and daily dialysis dose compared with a shorter (15–20 cm) catheter placed in the superior vena cava. Catheters should be placed with the use of ultrasound guidance because this allows for higher success of placement on the first attempt, less time for insertion, and fewer complications (see later section, Complications).

TABLE 67.4 Suggested Temporary Catheter Sizes for Pediatric Patients Based on Weight

Patient Weight or Size	Catheter Size
Neonate	Dual-lumen 7 Fr
3–6 kg	Dual-lumen 7 Fr
6–15 kg	Dual-lumen 8 Fr
15–30 kg	Dual-lumen 9–10 Fr
> 30 kg	Dual- or triple-lumen 11.5–12.5 Fr

From Sutherland SM, Alexander SR. Continuous renal replacement therapy in children. *Pediatr Nephrol*. 2012;27(11):2007–2016.

The best access, according to KDIGO recommendations, is as follows: right IJ vein, femoral vein, left IJ vein, and subclavian vein. Some studies have shown a higher incidence of complications, including infection, when the femoral vein is used. In adult intensive care unit (ICU), patients' jugular access does not appear to reduce the risk of catheter-related infections compared with femoral access, except in patients with a high body mass index. The subclavian vein should be avoided as the increased contact of the catheter with the wall of the vessel is associated with a higher risk of thrombosis and or stenosis. In children, a catheter in the IJ has been associated with better circuit survival compared with catheters placed in the femoral or subclavian vessels. Arteriovenous fistulas and grafts are not recommended for use in CRRT. The lower flow for a prolonged time can increase the risk of thrombosis, trauma, and needle dislodging, leading to bleeding. If a fistula or graft is used, plastic needles should be used and taped securely to prevent tears in the access site.

Common complications after catheter placement include hematoma, hemothorax and pneumothorax, thrombus formation, pericardial tamponade, air embolism, and retroperitoneal hemorrhage. Therefore, ultrasound guidance should be used for line placement, and before using an IJ or subclavian line, a chest radiograph should be obtained to check for correct positioning. Catheter-line infections are also a concern and should be avoided by placement under sterile technique and appropriate dressing and catheter care. The use of topical antibiotics at the skin insertion site and use of antibiotic locks are not suggested because they may promote fungal infections and antimicrobial resistance.

Dialyzer Membranes

Semipermeable hollow-fiber dialyzers are the standard of care for use during CRRT. All membranes lead to some degree of bioincompatibility with complement activation, proinflammatory marker release, and oxidative stress. In the past, older membranes made of cuprophane or unmodified cellulose could cause severe reactions leading to vasodilation, hypotension, hypoxia, fever, and leukopenia. The newer membranes are made of modified cellulose or synthetic materials such as polyacylnitrile, polysulfone, or polymethylmethacrylate, which are rarely associated with such reactions. Membranes are also classified as low and high flux. High-flux or high-permeability hemofilters have larger pores that can clear larger solutes (filter cut points of more than 60 kDa as opposed to 20–30 kDa) and allow for higher rates of fluid removal. KDIGO recommends the use of a biocompatible membrane or modified cellulose acetate membrane.

Of note, one of the biocompatible membranes, the AN-69 membrane, has been associated with the bradykinin release syndrome when blood priming of the extracorporeal circuit

TABLE 67.5 Composition of Commercial Replacement and Dialysate Solutions

	PrismaSate		PrismaSol					
	Ca	No Ca	Ca	No Ca	PrismOcal	Baxter Premixed	Duosol Bicarbonate 35 Dialysate 0K/3Ca	Duosol Bicarbonate 35 Dialysate 2K/3Ca
Intended use	D	D	RF	RF	D/RF	D for HDF	D	D
Citrate								
Sodium (mEq/L)	140	140	140	140	140	140	140	140
Chloride (mEq/L)	109.5–113	108–120.5	109–113	106.5–110.5	106	117	109	111
Bicarbonate (mEq/L)	32	22–32	32	32	32	0	35	35
Lactate (mEq/L)	3	3	3	3	3	30	0	0
Potassium (mEq/L)	0–4	2–4	0–4	0–4	0	2	0	2
Calcium (mEq/L)	2.5–3.5	0	2.5–3.5	0	0	3.5	3	3
Magnesium (mEq/L)	1–1.5	1–1.5	1–1.5	1–1.5	1	1.5	1	1
Dextrose (mmol/L)	0–6.1	0–6.1	0–5.6	0–5.6	0	5.6	1	1
Phosphate (mmol/L)								
SID	35	25–35	35	35	32	29	—	—
Number of compartments	2	2	2	2	2	1	2	2
Base in small compartment	N/A	N/A	Yes	Yes	Yes	—	Yes	Yes

Ca, Calcium; *D*, dialysate; *K*, potassium; *N/A*, not available; *RF*, replacement fluid; *SID*, strong ion difference, assuming that lactate is transformed into bicarbonate.
Updated from Claure-Del Granado R, Bouchard J. Acid–base and electrolyte abnormalities during renal support for acute kidney injury: recognition and management. *Blood Purif.* 2012;34(2):186–193.

is needed (e.g., in small children when the extracorporeal volume is >10%–15% of their blood volume). The syndrome is self-limited and pH dependent; it manifests more prominently in patients with severe acidosis, when banked blood is used, and in patients receiving angiotensin-converting enzyme (ACE) inhibitors. When the membrane is exposed to blood, bradykinin is released and leads to vasodilation, which can cause extreme hypotension within 5–10 minutes after starting CRRT; ACE inhibitors prevent the breakdown of bradykinin, leading to prolonged hypotension. Because of the potential for this serious complication, use of this membrane is generally avoided. However, other measures, such as normalizing banked blood pH or giving the patient (rather than the circuit) the blood prime, can prevent or decrease the reaction if no other membrane options are available.

Dialysate and Replacement Solutions

Many solutions are currently commercially available for use in CRRT. These solutions have varying amounts of sodium, potassium, chloride, glucose, phosphate, calcium, and magnesium (Table 67.5). The choice of solution should be based on the capacity to restore acid-base balance and physiologic electrolyte concentrations for the individual patient. Electrolyte adjustments may be needed depending on specific circumstances (e.g., hyperkalemic patients will initially need a solution with 0–2 mmol/L concentration of potassium). The pharmacy can also add electrolytes to customize the electrolyte composition, but there is a chance for error when this is done. Calcium is not included in solutions that contain phosphate because an insoluble precipitate may form. A buffer anion is also necessary in solutions because bicarbonate is lost through the hemofilter. Bicarbonate, acetate, lactate, and citrate are available, but bicarbonate is the preferred buffer (see later section, Correction of Acid-Base Abnormalities).

Anticoagulation

When blood comes into contact with the surface of the extracorporeal circuit, the intrinsic and extrinsic coagulation pathways and platelets become activated. Some form of continuous anticoagulation is, therefore, needed to prevent dialyzer or hemofilter clotting. Anticoagulation is recommended for AKI patients if they do not have an increased risk of bleeding or impaired coagulation or are not already being given systemic anticoagulation. If there are no contraindications to regional citrate, its use is recommended rather than heparin. When there are contraindications to citrate, unfractionated or low-molecular-weight heparin should be used. If heparin-induced thrombocytopenia (HIT) occurs, heparin should be stopped, and a direct thrombin

Duosol Bicarbonate 25 Dialysate 2K/0Ca	Duosol Bicarbonate 32 Dialysate 2K/0Ca	Duosol Bicarbonate 35 Dialysate 4K/3Ca	Duosol Bicarbonate 25 Dialysate 4K/0Ca	multiBic	Miltiplus	Ci-CaDialysate	Ci-Ca Dialysate Plus	MuilLac
D	D	D	D	RF	RF	D	D	RF
136	136	140	136	140	140	133	140	
115	107.5	113	117	109-11-112-113	111	115.75	113	
25	32	35	25	35	35	20	35	
0	0	0	0	0	0		0	
2	2	4	4	0-2-3-4	2	2-4	4	
0	0	3	0	1.5	1.5	1.5	1.5	
1.5	1.5	1	1.5	0.5	0.5	0.5	0.5	
0	0	0	0	1	1	1	1	
						1.25		
—	—	—	—	—	—	—	—	
2	2	2	2	2	2	1	2	
Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	

inhibitor (argatroban) or factor Xa inhibitor (danaparoid or fondaparinux) should be used instead. Prefilter replacement fluid can be used to prevent filter clotting when anticoagulation is not or cannot be used. More details on anticoagulation can be found in Chapter 68.

Treatment Dosing

The surrogate of solute removal in CRRT is the effluent rate that can be expressed in milliliters per kilogram per hour. Based on randomized controlled trials (RCTs), KDIGO guidelines recommend delivering an effluent dose of 20 to 25 mL/kg/h for patients with AKI; other references recommend a dose of 25 to 30 mL/kg/h. In 2000, Ronco and colleagues performed a prospective, randomized trial of CRRT UF dosing that compared doses of 20 mL/kg/h, 35 mL/kg/h, and 45 mL/kg/h in AKI ICU patients. They demonstrated that a dose of at least 35 mL/kg/h improved survival at 15 days after stopping CRRT compared with the lower dose; there was no significant difference in survival between patients receiving 35 mL/kg/h and those receiving 45 mL/kg/h. After this study, a dose of 35 mL/kg/h became the standard dose widely used.

These concepts changed after two large studies were published. The Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network (ARFTN) performed a large, multicenter study comparing standard-dose CVVHDF of 20 mL/kg/h with high-intensity CVVHDF of 35 mL/kg/h in critically ill AKI patients; it demonstrated no significant difference in 60-day all-cause mortality, rate of recovery of renal function, and duration of RRT. The Randomized Evaluation of Normal vs. Augmented Level (RENAL) Renal Replacement Therapy Study was another large, multicenter study comparing a CVVHDF effluent flow of 40 mL/kg/h to 25 mL/kg/h to see if there was a difference in 90-day mortality and continued need for RRT in ICU patients with AKI; there was no significant difference in either outcome between the two groups.

An international survey of intensivists reported that use of CRRT hemofiltration doses of at least 45 mL/kg/h was prescribed for septic AKI patients despite little recent evidence supporting this. As stated earlier, there is no difference in outcomes when using high-volume hemofiltration (HVHF) versus standard-volume hemofiltration in these patients.

An important caveat in assessing dose based on effluent volume is that during therapy, there is a progressive filter fouling and clotting that can lower the efficacy of solute removal. Thus, the true dose delivered may be significantly less than that estimated from the effluent volume. Measuring solute removal in the effluent and calculating clearance based on the mass extracted should be the gold-standard method to assess delivered dose. When considering the results of the studies on dialysis dose improving outcomes, it is important to remember that greater than or equal to 85% of the prescribed dose was delivered to AKI patients. This is usually much more than what is delivered in clinical practice (see Table 67.6 for factors that affect dose delivery). Therefore, when prescribing a treatment dose, clinicians should have at least a 25% safety margin; prescribing a dose of 30 to 35 mL/kg/h may then deliver an adequate dose.

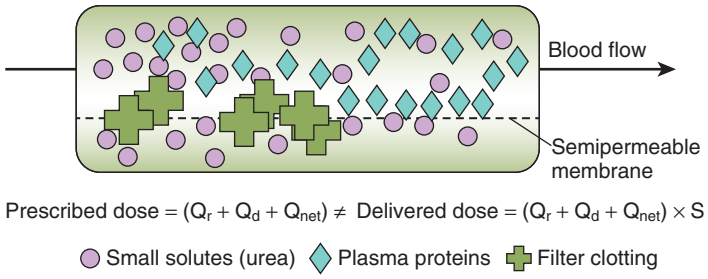
TABLE 67.6 Factors Affecting Continuous Renal Replacement Therapy Dose Delivery

Filter clotting or type of anticoagulation
Decreased sieving coefficient
Secondary membrane formation
Filtration Fraction and Concentration polarization
Changing catabolic rate/urea generation in AKI and critically ill patients
Catheter-related problems (type of catheter, site of placement, hygiene, etc.)
Circuit down-time (routine filter changes)
Time off for diagnostic procedures and therapeutic interventions

AKI, Acute kidney injury.

Factors That Impact Dialysis Dose

As noted earlier, filter permeability decreases over time; thus, effluent volume (derived from blood-based kinetics) can overestimate delivered clearance. Exposure of the membrane to plasma leads to adsorption and deposition of proteins on the membrane. Concentration polarization results from the accumulation of solute rejected by the UF membrane. Both phenomena result in a concentrated layer along the membrane, causing resistance to mass transfer. Higher filtration fraction and high volume of UF accelerate this process. Transmembrane pressure needs to be increased to maintain an adequate Q_{uf} to overcome this and lower the concentration of important solutes in the effluent. A second factor is progressive filter clotting, which decreases the SC and filters permeability. The decrement in permeability can be measured by the ratio of effluent fluid urea nitrogen (FUN) to blood urea nitrogen (BUN), which at the beginning of the filter life is equal to 1 and progressively decreases with filter clotting. The CRRT machine measures effluent volume but cannot take into account changes in filter permeability (Fig. 67.2). The FUN-to-BUN ratio should be measured at least daily to assess the dose in the CRRT. Table 67.7 shows the calculations to assess dialysis dose in CRRT. These calculations help correct dialysis prescriptions with regard to small solute clearance, but changes in filter permeability also affect middle molecule clearance. It has been suggested that future studies include measured clearances of small and middle molecules to determine the actual delivered dose. Because the effluent rate provides only an inaccurate estimate of the



• **Fig. 67.2** The effect of concentration polarization and clotting on delivered dialysis dose. Filter efficacy declines over time; protein fouling and filter clotting occur on the membrane and decrease the surface available for diffusion or convection, which reduces the amount of dose being delivered. These important factors must be frequently monitored during continuous renal replacement therapies. *BUN*, Blood urea nitrogen; *FUN*, effluent fluid urea nitrogen; Q_d, dialysate fluid rate; Q_{net}, net fluid removal rate; Q_r, replacement fluid rate; *S*, FUN/BUN ratio. (From Macedo E, Claure-Del Granado R, Mehta RL. Effluent volume and dialysis dose in CRRT: time for reappraisal. *Nat Rev Nephrol*. 2012;8(1):57-60.)

TABLE 67.7 Continuous Renal Replacement Therapy Dose Assessment

CVVH

Prescribed dose = $Q_r + Q_{net}$

Delivered dose = $(Q_r + Q_{net}) \times (FUN/BUN)$

CVVHDF

Prescribed dose = $Q_r + Q_d + Q_{net}$

Delivered dose = $(Q_r + Q_d + Q_{net}) \times (FUN/BUN)$

Correcting for predilution effect

Delivered dose = $Q_{net} \times ([Q_{bw}/\{Q_{bw} + Q_r\}] + Q_d \times [Q_{bw}/\{Q_{bw} + Q_r\}]) \times (FUN/BUN)$

$Q_{bw} = (1 - \text{hematocrit}) \times Q_b$.

BUN, Blood urea nitrogen; *CVVH*, continuous venovenous hemofiltration; *CVVHDF*, continuous venovenous hemodiafiltration; *FUN*, effluent fluid urea nitrogen; Q_{bw}, blood-water flow rate; Q_d, dialysate fluid rate; Q_{net}, net fluid removal rate; Q_r, replacement fluid rate.
Adapted from Macedo E, Claure-Del Granado R, Mehta RL. Effluent volume and dialysis dose in CRRT: time for reappraisal. *Nat Rev Nephrol*. 2012;8(1):57–60.

delivered dose, in 2012, Claure-Del Granado et al. actually recommend measuring and expressing the delivered dose as urea clearance (K_D or K_{urea}), derived from dialysate-side kinetics. This is the ratio of mass removal rate to blood concentration and is calculated using the formula: K delivered = (FUN × EV)/BUN, where FUN is urea nitrogen in the effluent (mg/dL), BUN is urea nitrogen in the plasma (mg/dL), and EV is the effluent volume (mL/min). K_D takes into account filter function, duration, and effective time of treatment. They also suggest that the equivalent renal urea clearance (EKR), based on urea kinetic modeling, provides a good estimate of delivered dialysis dose (please see reference for calculating EKR) and can be used as a tool to compare different types of therapies. These recommendations are based on findings evaluating six different methods of assessing and expressing CRRT delivered dose (three equations from blood-side kinetics and three equations from dialysate-side kinetics) in critically ill AKI patients treated with predilution CVVHDF and regional citrate anticoagulation. The dialysate-side measurement ensures delivery of dose, and the blood-side measurement helps determine if changes need to be made in the prescription.

Other factors can also affect the delivered dose. The use of predilution is a third factor, which may decrease urea clearance by as much as 15%. Using replacement fluid prefilter reduces the concentration of solutes in the plasma and decreases solute clearance. Table 67.6 lists other factors impacting dose delivery.

Fluid Management

CRRT is highly effective for fluid control. Fluid balance can be maintained without compromising metabolic–solute balance because they can be dissociated from each other. Fluid removal in CRRT is achieved through manipulating the UFR, which can be tailored to individual needs. The net ultrafiltrate is the difference between total ultrafiltrate (the plasma water removed) and total substitution (the fluid given to the patient) through the CRRT machine. CRRT machines balance all the fluids removed and replaced across the dialysis circuit in order to generate a net amount of fluid removal. All intakes and outputs need to be included to achieve patient fluid balance and integrated into machine and patient fluid prescription and delivery.

Bouchard and Mehta describe three techniques for achieving fluid balance with CRRT (Table 67.8). The level 1 technique is to vary the net UFR (Q_{uf}) to meet the anticipated fluid balance needs over 8 to 24 hours; for example, a patient may have a total anticipated fluid intake of 3 L with desired 1-L net loss over 24 hours; the Q_{uf} would be set at −170 mL/h (3 L + 1 L = 4 L/24 h). This may not be the best technique to use because there may be unanticipated changes in clinical status and fluid needs, leading to a different net ultrafiltrate that is different from the desired fluid balance. In addition, effluent volume and treatment dose will vary because net Q_{uf} is not constant with this method.

TABLE 67.8 Continuous Renal Replacement Therapy Fluid Balance Techniques

Variable	Level 1	Level 2	Level 3
Intake	Variable	Variable	Variable
Non-CRRT output	Variable	Variable	Variable
Ultrafiltration rate	Variable to achieve fluid balance	Fixed to achieve target effluent volume	Fixed to achieve target effluent volume
Substitution fluid rate	Fixed = or < Q_{uf}	Postdilution replacement varies to achieve −, zero, or + fluid balance	Postdilution replacement varies to achieve −, zero, or + fluid balance
Fluid balance	Achieved by varying Q_{uf}	Achieved by adjusting amount of substitution fluid	Targets the hourly fluid balance to achieve a predefined hemodynamic parameter
Key difference	Output varies to accommodate changes in intake and fluid balance goals	Output is fixed to achieve desired solute clearance and allow flexibility in accommodating varying intake	Output is fixed to achieve desired solute clearance and allow flexibility in accommodating varying intake
Examples	SCUF, CVVHD	CVVH, CVVHDF	CVVH, CVVHDF
Advantages			
Patient factors	Strategy similar to fluid removal in intermittent dialysis	Solute clearance is constant. Allows variation in intake. Individualizes prescription.	Solute clearance is constant. Allows variation in intake. Individualizes prescription.
CRRT factors	Fluid balance calculations can be deferred to longer intervals (every 8–12 hours)	Clearance requirements dissociated from fluid balance. Decreases interactions with CRRT pump to adjust UFR. Regimen simplified for caregiver.	Clearance requirements dissociated from fluid balance. Decreases interactions with CRRT pump to adjust UFR. Regimen simplified for caregiver.
Disadvantages			
Patient factors	Patient assumed to be in static state. Similar to ESRD prescription. Intake may fluctuate. Fluid boluses not accounted for. Commonly over- or undershoot. Fluctuations in solute clearance, especially when dependent on convection.	Requires hourly calculations for the amount of fluid replacement to be given. Potential for fluid imbalances if balance sheet not used.	Requires hourly calculations for the amount of fluid replacement to be given. Potential for fluid imbalances if balance sheet not used. Requires scale be made for hemodynamic parameter targets.
CRRT factors	Requires frequent interactions with CRRT pump to adjust UFR. Underutilizes CRRT for fluid removal only.	Requires use of external pump to achieve fluid regulation.	Requires use of external pump to achieve fluid regulation.

CRRT, Continuous renal replacement therapy; *CVVH*, continuous venovenous hemofiltration; *CVVHD*, continuous venovenous hemodialysis; *CVVHDF*, continuous venovenous hemodiafiltration; Q_{uf}, ultrafiltration rate; *SCUF*, slow continuous ultrafiltration.
Adapted from Bouchard J, Mehta RL. Volume management in continuous renal replacement therapy. *Semin Dial.* 2009;22(2):146–150.

The level 2 method of maintaining fluid balance is to vary the amount of postdilution replacement fluid administered; the net ultrafiltrate stays the same and exceeds the anticipated hourly intake. With this technique, the postdilution fluid is not given through the CRRT pump but through a separate pump. A patient can be maintained in negative fluid balance by decreasing the amount of postdilution fluid received to be less than the total output, in positive fluid balance by increasing postdilution replacement to be greater than all output, or in even balance by having equal postdilution replacement and total output. This method allows for variation in intake and a predetermined convective clearance because net ultrafiltrate does not vary as in the first technique.

The level 3 technique is similar to the second, but fluid balance is tailored to achieve a targeted hemodynamic parameter every hour. Predefined targets are set for parameters, such as central venous pressure (CVP), mean arterial pressure (MAP), or pulmonary arterial wedge pressure, and algorithms are used to achieve these targets. For example, if the CVP is to be maintained between 8- and 12-mm Hg when this is achieved, the algorithm would determine that net fluid balance be set to zero. If the CVP is above target, the algorithm would call for fluid removal; if CVP is below

target, then fluid would be added. This technique allows for greater flexibility and maximally uses CRRT as a fluid regulatory device.

Applications

Continuous RRT has been offered to sicker and hemodynamically unstable patients in the ICU setting. However, studies designed to compare continuously versus intermittent therapies have not shown a beneficial effect on mortality. On the other hand, several CRRT characteristics favor its use, including the longer duration of therapy, allowing slow fluid with greater hemodynamic stability, and a higher likelihood of kidney recovery compared to standard IHD.

Nevertheless, the choice of which modality to use in critically ill AKI patients is based largely on available resources and experience with a specific modality. The 2012 KDIGO Clinical Practice Guideline for AKI recommends using CRRT and intermittent RRT (IRRT) as complementary therapies. However, for critically ill patients with hemodynamic instability, KDIGO suggests using CRRT. It offers the advantages of: slower fluid removal for better hemodynamic stability and control of fluid balance; slower changes in solute concentrations to prevent large fluctuations and fluid shifts; ability to remove fluid restrictions, which allows for proper nutrition, medications, and blood product administration; and the flexibility to adapt to a patient's changing treatment needs.

When managing AKI patients with any form of RRT, the goals of therapy must be defined. In patients with end-stage kidney disease (ESKD), the aim is to postpone starting dialysis until a substantial amount of renal function is lost. This should not be the strategy used for patients with AKI, however. RRT for these patients should be thought of as a way to prevent or halt the rapid decline in renal function and support other organs to allow time for recovery. In this way, RRT provides renal support rather than renal replacement. Table 67.9 lists potential applications for CRRT.

TABLE 67.9 Potential Applications for Continuous Renal Replacement Therapy in Patients With Acute Kidney Injury

Renal Replacement	Renal Support
Acute kidney injury	Fluid management
Chronic renal failure	Solute and electrolyte management
	Acid–base management
	Nutrition
	Sepsis, cytokine removal, or multiple organ failure

Traditional and Special Indications for Treatment

CRRT can be applied not only when patients meet standard criteria for IHD: hyperkalemia, severe acidosis, volume overload, severe uremia leading to complications, pronounced azotemia, severe oliguria or anuria, and drug intoxications. However, in practice, CRRT is often used only when the patient is hemodynamically unstable. We suggest that CRRT should be considered for critically ill patients, even when the patient is hemodynamically stable, as it provides the opportunity to adjust solute and fluid balance on an ongoing basis. Other indications for which CRRT may be started include sepsis, increased intracranial pressure (ICP), heart failure, correction of severe electrolyte and acid-base abnormalities, and removal of poisons. Table 67.10 includes contraindications to starting CRRT, and Table 67.11, other factors that influence the decision to start RRT.

TABLE 67.10 Indications and Contraindications for Continuous Renal Replacement Therapy in Critically Ill Acute Kidney Injury Patients

Indications

Classic indications
- Hyperkalemia
- Severe metabolic acidosis
- Diuretic-resistant volume overload
- Oliguria or anuria
- Uremic complications
- Some drug intoxications

Potential indications
- Hemodynamic instability
- Disrupted fluid balance (caused by cardiac failure or multiorgan failure)
- Increased ICP
- Electrolyte abnormalities

Contraindications

- Advance directives indicating that the patient does not want dialysis
- The patient or their health care proxy declines continuous RRT
- Inability to establish vascular access
- Lack of appropriate infrastructure and trained personnel for continuous RRT

ICP, Intracranial pressure; *RRT*, renal replacement therapy.
From Tolwani A. Continuous renal-replacement therapy for acute kidney injury. *N Engl J Med.* 2012;367(26):2505–2514.

TABLE 67.11 Factors Influencing Initiation of Renal Replacement Therapy in Acute Kidney Injury

Patient safety
Unnecessary procedure
Possibility of patient recovering renal function
Risk associated with RRT procedure
Complications associated with catheter placement
Hypotension and cardiac events during procedure
Fear of prolonging renal injury after initiation of RRT
Factors affecting implementation
Logistics
Vascular access availability
Availability of equipment and personnel
Time of decision to initiation (Sundays, late night)
Treating physician decision

RRT, Renal replacement therapy.
From Macedo E, Mehta RL. Tailored therapy: matching the method to the patient. *Blood Purif.* 2012;34(2):124-131.

Septic Acute Kidney Injury

Sepsis is the main cause of AKI in the ICU. About 30% to 50% of septic AKI patients need some form of RRT. Sepsis-associated AKI (SAKI) is preferably treated with continuous therapies for the reasons stated earlier. In addition, CRRT allows for temperature and acid-base status control. It could also be thought of as organ support for SAKI, such as in patients with acute respiratory distress syndrome (ARDS); CRRT has been shown to improve and stabilize oxygenation, decrease the duration of mechanical ventilation, and decrease cytokine levels in the blood.

In patients with multiple-organ dysfunction, CRRT has been used as a modulator of the immune response. The effects of CRRT on modulating levels of inflammatory mediators have been studied for 2 decades. Newer, high-flux membranes have the ability to remove inflammatory mediators, such as cytokines and chemokines, by convection. Using conventional CRRT techniques, however, may not be of clinical significance because these mediators have high turnover rates. Different techniques have been developed: HVHF, high adsorption hemofiltration, high-cutoff membranes, and hybrid systems such as coupled plasma filtration absorbance. Experimental and small clinical studies of humans have suggested that HVHF might improve hemodynamic profile and mortality, but larger trials did not confirm this effect. A meta-analysis of different studies has shown that cytokines are insignificantly removed by hemofiltration techniques. Studies involving the use of HVHF have been conducted to see if clinically significant removal of inflammatory mediators can be achieved. In the IVOIRE (High Volume Hemofiltration for Sepsis with AKI) trial, HVHF at 70 mL/kg/h showed no benefit on mortality, early improvements in hemodynamic profile, or organ function as compared to contemporary standard volume hemofiltration at 35 mL/kg/h.

High cutoff membranes, which have larger pore sizes, have better cytokine removal compared with standard high-flux membranes; this has been noted in ex vivo studies, animal experiments, and preliminary clinical studies. They also have favorable effects on immune cell function and increase survival in animal models of sepsis. Based on these concepts, extracorporeal blood purification has been proposed as an adjuvant therapy for sepsis, with the goal of controlling the associated dysregulation of the immune system. Most devices for blood purification focus on endotoxin removal, aiming to avoid the stimulus of the cytokine storm. New highly adsorptive membranes can combine cytokine and endotoxin removal properties, renal replacement function, and antithrombogenic properties. More recently, promising treatments that focus on the pathogen itself or the immune cells have been developed and are currently under investigation. Despite the great progress on extracorporeal therapies, further research is needed to clarify their mechanisms of action and clinical benefits.

Increased Intracranial Pressure

AKI is a frequent complication in patients with acute brain injury (ABI) and liver failure patients with hepatic encephalopathy. In the patient with a high risk for increased ICP, the rapid urea removal that occurs in conventional IHD can cause a rapid decline in plasma osmolality and shift of fluid to the intracellular compartment, worsening brain edema and exacerbating the reduction in cerebral perfusion. The phenomenon is known as dialysis disequilibrium syndrome. Reduced intensity of dialysis leads to slower urea removal and increases the time for osmotic gradient adjustment in the brain. The goal for ABI and increased ICP patients are to maintain cerebral perfusion pressure (CPP) above 60 mm Hg; this is done by ensuring that MAP stays up because CPP = MAP – ICP. With IHD, intradialytic hypotension is common, leading to decreased MAP and CPP and increased ICP by compensatory cerebral vasodilation. This may result in infarction or secondary brain injury. Decreased CPP and dialysis disequilibrium can be avoided with CRRT's slow, steady fluid and solute removal. This was demonstrated in a report by Ronco et al., in which there was increased brain density or water content on computed tomography (CT) scans in all patients after IHD but no change in density in patients who had CVVH.

For patients with ABI or increased ICP, KDIGO suggests using CRRT rather than IHD.

Hypertonic saline infusions have been used to attenuate the problem of dialysis disequilibrium. The high osmotic content can temporarily produce an osmotic force to draw fluid from the brain parenchyma to the intravascular compartment, improving cerebral edema and ICP. Unfortunately, however, it can lead to volume overload and decreased oxygenation.

Another advantage of CVVH or CVVHDF is the ability to maintain hypernatremia while keeping the patient euvolemic or in negative fluid balance. High-dialysate sodium concentrations or addition of sodium to replacement solutions is the key. It is recommended that a sodium concentration of at least 140 mEq/L be used during treatment, although a target of about 150 to 160 mEq/L is not uncommon.

Heart Failure and Cardiorenal Syndrome

Acute decompensated heart failure (ADHF) accounts for more than 1 million hospitalizations yearly. Diuretics are still the mainstay of therapy, but hypotension, diuretic resistance, and decreased kidney function have led clinicians to use various forms of extracorporeal therapy.

The Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure trial (UNLOAD) study compared outcomes between patients who received standard diuretic treatment versus slow intermittent UF, although patients with serum creatinine of 3 mg/dL or greater were excluded. UF patients had greater weight loss at 48 hours and lower hospital readmission and emergency department visit rates at 90 days. However, the Cardiorenal Rescue Study in Acute Decompensated Heart Failure trial (CARESS-HF), which compared the effect of UF versus stepped pharmacologic therapy on renal function and weight (also excluded patients with serum creatinine ≥ 3.5 mg/dL), revealed different results. There was no difference in weight loss or readmission rates between the two groups; there was also an increased risk of AKI in the UF group.

In 2015, Prins et al. studied in-hospital mortality in patients with ADHF requiring inotropes or vasopressors (or both) and CRRT for severe AKI (cardiorenal syndrome 1). CRRT was performed with CVVHDF and an effluent rate of 25 to 30 mL/kg/h. They found that CRRT in this setting was associated with high in-hospital mortality; most patients did not recover renal function (even with volume removal), and long-term prognosis was poor. The AVOID-HF trial showed a trend toward a longer time to a new event of heart failure decompensation, with significantly fewer patients being rehospitalized for heart failure or cardiovascular causes at 30 days in the UF group. The results suggest no negative impact on kidney function with excess fluid removed with managed UF. Nevertheless, a number of questions and concerns are still unresolved, including the need for anticoagulation, complications related to the extracorporeal circuit, and the effect of UF on kidney function and long-term outcomes. In the context of available evidence from these RCTs, cost, and complexity of therapy, UF cannot currently be recommended as a first-line therapy for ADHF.

Correction of Severe Electrolyte Abnormalities

An important benefit of CRRT is that plasma electrolyte concentration can be safely maintained at any specific desired range by adjusting the composition of the substitution fluids and dialysate.

Hypo- and Hypernatremia

In chronic hyponatremia, it is safer to avoid correction of sodium faster than an 8 mEq/L increment in 24 hours. With CRRT, lower volumes of replacement and/or dialysate fluid per hour can be used and/or sodium levels can be customized. Sodium content in replacement fluid is 140 mEq/L, so to correct hyponatremia, 5% dextrose in water (D5W) can be infused separately to slowly increase sodium levels. As an example:

$$\text{Target sodium concentration} = 123\ \text{mEq/L}$$

$$\text{Replacement fluid sodium content} = 140\ \text{mEq/L}$$

$$\text{D5W sodium content, peripheral} = 0\ \text{mEq/L}$$

$$\text{Desired clearance} = 2.5\ \text{L/h}$$

$$\text{Replacement fluid rate} = \frac{\text{Target sodium concentration}}{140} \times \text{Desired clearance} = \frac{123}{140} \times 2.5\ \text{L/h} = 2.2\ \text{L/h}$$

$$\text{D5W rate} = \frac{(140 - \text{Target sodium concentration})}{140} \times \text{Desired clearance} = \frac{(140 - 123)}{140} \times 2.5\ \text{L/h} = 0.3\ \text{L/h} = 300\ \text{mL/h}$$

As stated earlier, some neurologic conditions may benefit from keeping a patient hypernatremic. In these cases, infusing NaCl 3% separately or adding NaCl or $NaHCO_3$ directly to replacement fluid can be done. As an example:

$$\text{Target sodium concentration} = 150\ \text{mEq/L}$$

$$\text{Replacement fluid sodium content} = 140\ \text{mEq/L}$$

$$\text{NaCl 3\% sodium content, peripheral} = 513\ \text{mEq/L}$$

$$\text{Desired clearance} = 2.5\ \text{L/h}$$

$$\text{NaCl 3\% rate} = \frac{(\text{Target sodium concentration} - 140)}{513} \times \text{Desired clearance} = \frac{(150 - 140)}{513} \times 2.5\ \text{L/h} = 0.05\ \text{L/h}$$

$$\text{Replacement fluid rate} = \text{Desired clearance} - \text{NaCl 3\% rate} = 2.5\ \text{L/h} - 0.05\ \text{L/h} = 2.45\ \text{L/h}$$

In both situations, serum sodium levels should be checked every 2 hours to ensure correction is not too rapid.

Hypo- and Hyperkalemia

CRRT is an option for hyperkalemia when cardiac conduction is not affected, there is no emergent need to decrease potassium levels, and patients cannot tolerate intermittent therapy. Increasing the volume of replacement fluid or dialysate solution, in addition to using a solution with zero or low (2 mEq/L) potassium concentration, improves potassium removal. Serum potassium levels should be monitored frequently, every 2 to 6 hours, according to the severity of hyperkalemia and the expected rate of correction, especially if zero-potassium solutions are used.

Hypokalemia is a less frequent issue in AKI but can often be a complication of prolonged CRRT. CRRT replacement fluid should contain 3 to 4 mEq/L of potassium to prevent hyprokalemia. Correction of hypokalemia is the same as in patients not on RRT with potassium boluses and by increasing potassium concentration in dialysate and replacement solution.

Other Electrolytes

Hypocalcemia, hyperphosphatemia, and mild hypermagnesemia are also commonly seen in AKI patients. Calcium concentration in CRRT dialysate and replacement fluids varies from 0 to 2.5–3.5 mEq/L. The choice of the concentration depends on the anticoagulation used and calcium blood levels.

Magnesium can also be controlled by CRRT; normal concentration ranges from 1 to 1.5 mEq/L and can be increased in patients with prolonged therapy or poor nutrition.

Most dialysate and replacement fluids do not contain phosphate. Hypophosphatemia is a common complication in a patient with prolonged CRRT. Phosphate can be replaced orally in patients that are not on oral restrictions or IV if NPO or levels below 1 mmol/L.

Correction of Acid-Base Abnormalities

Metabolic Acidosis

Acid-base disorders are common in AKI patients, resulting from the inability to regenerate bicarbonate and excrete ammonium ions. In some patients, bicarbonate and pH levels may be normal; thus, calculating the anion gap is important to help identify the cause of metabolic acidosis. Bicarbonate, lactate, citrate, and acetate are the four buffers in dialysis and replacement solutions used to treat acidosis. Acetate, however, is no longer used because it negatively affects hemodynamics and does not correct acidosis as well as the other buffers.

Bicarbonate is the most frequently used buffer. Bicarbonate concentrations in CRRT solutions are lower than in IHD, normally ranging from 25 to 35 mEq/L. The highest concentration of bicarbonate should be used to stabilize levels; then, the dose can be titrated based on the patient's needs to control acidosis. It is important to recognize that CRRT will lead to bicarbonate removal equivalent to the small solute clearance and these losses need to be considered when dosing CRRT.

Bicarbonate and lactate are equivalent in their ability to correct acidosis. Lactate is less expensive and more stable. In patients with liver failure, however, or lactic acidosis and shock, the slow hepatic metabolism of lactate to bicarbonate can cause lactate accumulation. Another option for CRRT base is citrate, an anticoagulant and a buffer. Its use can lead to metabolic alkalosis, especially in higher doses, as 1 mmol of citrate is converted to 3 mmol of bicarbonate. Again, caution should be used in patients with liver failure because citrate conversion to bicarbonate may be decreased. Citrate can be delivered prefilter concurrently with UF to prevent fluid overload.

Metabolic Alkalosis

Metabolic alkalosis can also occur in AKI patients, although it is most often found as a complication of citrate anticoagulation. The use of 4% trisodium citrate for circuit anticoagulation can lead to excessive sodium load and hypernatremia. As citrate is metabolized to bicarbonate, there may be metabolic alkalosis during or after prolonged treatment.

Other causes of metabolic alkalosis include diuretic use, posthypercapnia in ventilated patients, and transfusion of blood products that contain citrate. Management includes decreasing the bicarbonate concentration in solutions to the lowest concentration available. Custom-made bicarbonate solutions may be made by the pharmacy. Chloride concentration in solutions should also be increased, and if sodium levels are high, sodium concentration should be decreased.

Respiratory Acidosis and Alkalosis

AKI can be seen concurrently in patients with ARDS. These patients are often treated with permissive hypercapnia, which leads to respiratory acidosis. CRRT permits adjustment of bicarbonate and pH levels in conjunction with a patient's pCO_2. Respiratory alkalosis is treated like metabolic alkalosis by decreasing the bicarbonate concentration in solutions to maintain normal pH.

Removal of Poisons

CRRT can effectively remove some drugs and toxins, but the clearance is often faster and can be more efficiently achieved with IHD, the usual treatment of choice. Solute clearance depends on blood/dialysis flow rate(s) and membrane characteristics, as well as the molecular weight (MW) of the solute, the proportion of solute bound to plasma protein, and volume of distribution (VD) of the solute. For example, a molecule that is large or highly protein bound and has a large VD is not cleared as well as a low-MW solute that is not bound to protein and has a small VD.

The advantage of using CRRT is that it can be tolerated by hemodynamically unstable patients. Molecules as large as 20,000 to 40,000 Da can be cleared through CRRT membranes, but the clearance rate is lower compared with IHD. Because of slower clearance, there is usually no rebound of compounds removed from the blood with CRRT.

Lithium poisoning is one of the situations in which CRRT is a viable alternative to IHD. This mood stabilizer drug has a low MW (<7 Da) that is not protein bound and has a VD of 0.6 to 0.9 L/kg. Altered mental status, clonus, and muscle fasciculations are signs of poisoning. The mainstay of treatment is administration of normal saline to enhance elimination. Extracorporeal treatment (ECTR) is recommended when there is AKI and the lithium concentration is greater than 4 mEq/L, or if decreased level of consciousness, seizures, or life-threatening dysrhythmias occur irrespective of the concentration; it is suggested, if the concentration is greater than 5 mEq/L, significant confusion is present, or it is expected to take more than 36 hours to achieve a concentration of less than 1 mEq/L. CRRT can also be used after a session of IHD. Leblanc et al. found that lithium could be cleared at 48 to 62 mL/min with CVVHDF; clearance with IHD is 70 to 170 mL/min. They also noted that rebound did not occur and concluded that CVVHDF could be used when chronic poisoning occurred. Treatment should be continued until there is clinical improvement or the concentration is less than 1 mEq/L.

Acetylsalicylic acid (aspirin) has an MW of 138 Da, is 90% protein bound at therapeutic levels, and has a VD of 0.17 L/kg. Toxicity can lead to multiorgan dysfunction, especially metabolic acidosis and neurotoxicity. It is metabolized by the liver and excreted by the kidneys. Overdose is treated with activated charcoal and urinary alkalization. A systematic review of ECTR for salicylate poisoning by the EXTRIP Workgroup recommends ECTR if its concentration is greater than 100 mg/dL, if there is AKI and the concentration is greater than 90 mg/dL, if there are mental status changes, and if oxygen therapy is needed for hypoxemia. When standard therapy fails, ECTR is suggested if the concentration is greater than 90 mg/dL, if there is AKI and the concentration is greater than 80 mg/dL, or if blood pH is 7.2 or less. IHD is the treatment modality of choice, but CRRT is an option if IHD is not available or the patient is unstable. Treatment cessation is indicated if there is clinical improvement, if the concentration is less than 19 mg/dL, or if treatment has lasted at least 4 to 6 hours when salicylate levels are not available.

Carbamazepine, an anticonvulsant, is moderately dialyzable. It has an MW of 236 Da, is 75% to 78% protein bound, and has a VD of 0.8 to 1.8 L/kg. Toxicity may present with ataxia, seizures, tremors, drowsiness, slurred speech, or oliguria. It is remediated with activated charcoal. The EXTRIP Workgroup also performed a systematic review of ECTR for carbamazepine poisoning and suggested IHD as the preferred choice in severe poisoning; if this is not available, CRRT can be performed. One case report used albumin-enhanced CVVHDF to remove carbamazepine successfully; 25% albumin was added to the dialysate to adsorb the drug and maintain a concentration gradient; conventional CVVHDF would not be expected to clear the drug as well. ECTR is recommended if multiple seizures refractory to treatment or life-threatening dysrhythmias occur; it is suggested if prolonged coma or respiratory depression requires mechanical ventilation or if concentrations rise or stay elevated after use of multiple-dose charcoal and support measures. Treatment can be stopped after clinical improvement is noted or when the concentration is less than 10 mg/dL.

Monitoring and Complications

Hypothermia can be a common complication in CRRT when replacement fluids and dialysate are not warmed, leading to cooling of core body temperature. Newer CRRT machines have warming devices to prevent heat loss. Body temperature cooling can mask fevers, delaying infection recognition and treatment. In some instances, however, such as hypothermia, after cardiac arrest, or with brain injury, this cooling effect may be advantageous.

Electrolyte complications result from their removal by dialysis or hemofiltration, and insufficient replacement occurs, as well as from the use of citrate anticoagulation, as discussed in Chapter 68. Table 67.12 lists the potential electrolyte complications of CRRT. If severe derangements are present, laboratory measurements should be done frequently, about every 2 to 4 hours. Otherwise, electrolytes can be monitored at least every 6 hours and decreased to every 12 hours when they are stable.

When managing fluid status, monitoring for volume depletion is essential. This can occur if there is inadequate monitoring or inaccurate calculations are performed. Vigilant monitoring is important because there is the potential to

TABLE 67.12 Electrolyte Derangements With Continuous Renal Replacement Therapy

Derangement	Cause
Hypophosphatemia	Removal and inadequate replacement
Hypokalemia	Removal and inadequate replacement
Hypernatremia	Sodium citrate anticoagulation without lowering dialysate or replacement fluid sodium concentration
Hypocalcemia	Citrate anticoagulation and inadequate replacement
	Excessive citrate in hepatic failure patients
Hypercalcemia	Citrate anticoagulation and excessive calcium replacement
Hypomagnesemia	Removal and inadequate replacement

Adapted from Fall P, Szerlip HM. Continuous renal replacement therapy: cause and treatment of electrolyte complications. *Semin Dial.* 2010;23(6):581–585.

remove large amount of fluid quickly. Drops in blood pressure, tachycardia, or change in invasive monitoring (e.g., a decrease in CVP) are signs of volume depletion. Flow sheets for recording and monitoring fluid balance should always be used, and the nurse-to-patient ratio should be appropriate to ensure good-quality patient management.

Nutritional losses in critically ill patients on CRRT are common. These patients are likely to be hypercatabolic and in need of extra nutrition. Amino acid losses range from 10 to 20 g/day. Severe protein-energy wasting may ensue, leading to loss of lean body mass, reduction of fat mass, and low urea concentrations; all of these worsen in-hospital mortality rates, extend hospital stays, and increase the likelihood of infectious complications. Patients should receive increased daily protein or amino acid intake to about 1.5 to 2.5 g/kg/day. Glucose loss also occurs but is not well documented. Dialysate and replacement solutions contribute up to 40 to 80 g/day, although they do not usually lead to hyperglycemia. If glucose-free solutions are used, there is a risk of hypoglycemia or inadequate nutrition. For adequate intake, carbohydrates should be given at 5 to 7 g/kg/day. CRRT readily removes vitamins and minerals. Their supplementation has not shown a benefit on survival, but they still should be replaced, especially because water-soluble vitamins and active vitamin D are easily depleted. Of note, vitamin A supplementation is not recommended because its accumulation can be toxic. In addition, vitamin C intake should not exceed the recommended daily dose because it can lead to oxalosis.

Finally, drug clearance may be significantly impacted by CRRT. High CRRT doses influence the pharmacokinetics and pharmacodynamics of medications. Therefore, patients may be underdosed, especially with regard to antimicrobials, vasoactive medications, sedatives, paralytics, or antiseizure medications. Medications should be titrated based on effect, or when available, medication levels in the blood should be followed to adjust doses.

Outcomes

Despite the earlier-mentioned advantages of CRRT, RCTs have failed to show improvement in patient outcomes with CRRT as compared to IHD. Nevertheless, the wide variability and standards for CRRT use and the exclusion of more severely ill patients may have affected the results of these trials.

Despite a great number of RCTs and meta-analyses, there is a lack of solid evidence showing the superiority of any mode of RRT in patients with severe AKI in terms of patient survival. However, observational data have shown that IHD treatment of AKI may delay renal recovery. In 2017, Schoenfelder et al. conducted a systematic review of the literature and analyzed 49 studies. Findings showed a higher rate of renal recovery among survivors who initially received CRRT as compared with IHD. Economic analyses indicate that initial CRRT is cost-effective as compared with initial IHD when the costs of long-term dialysis dependence are considered. Nevertheless, patients' hemodynamic status, medical conditions, and availability of staff and resources should be considered for modality selection.

Allegretti and colleagues analyzed a prospective cohort of ICU patients started on CRRT with AKI at a single center to examine renal recovery and in-hospital and postdischarge mortality rates. They found that only 25% of AKI patients were dialysis free at the end of the follow-up period (4 years of rolling postdischarge data). While in the hospital, the mortality rate was about 61%; after discharge, about 28% of patients died. The total rate of renal recovery was 93% by the end of the study period.

Wald et al. performed a retrospective cohort study matching 1:1 CRRT and IRRT patients with AKI in the ICU. Only patients who survived past 90 days after RRT initiation were followed for a median duration of 3 years. It was found that chronic dialysis risk was lower in those patients who received CRRT versus IRRT (hazard ratio, 0.75; 95% confidence interval, 0.65–0.87). These results confirmed the findings of Schneider and colleagues' review and meta-analysis.

Data for children regarding mortality have been gathered from the Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT). The overall mortality rate was 42%. Survival was lowest for patients who had fluid overload and electrolyte imbalances at CRRT initiation. Children weighing more than 10 kg and those older than 1 year of age had better overall survival rates. Other reviews and observational studies that have shown worse outcomes seem to be associated with greater burden of illness, multiple organ involvement, and hemodynamic instability. In addition, infant survival has been consistent between about 35% and 45%, and infants weighing less than 3 kg have worse survival, around 24% compared with infants over 3 kg (41%) as reported by Symons et al. in 2003.

At the moment, CRRT and IRRT should be viewed as complementary therapies in patients with AKI. Because transitions between therapies reflect patient progression in the disease course, all the therapies should be considered as part of the nephrologists' armamentarium and used to support patients through their course. Monitoring of patient's hemodynamic status and adjustment of the therapy based on clinical criteria are essential for providing the best therapy with IHD or CRRT. The choice of therapy should also consider the familiarity and comfort of personnel with the technique, the UF volume necessary to achieve fluid balance, and the need for mobilization and physiotherapy.

Cost

CRRT costs per therapy are usually higher than for IRRT. However, cost analysis for AKI should consider in-hospital ICU costs and costs related to long-term dialysis dependence and nonrenal recovery.

In 2015, Ethgen and colleagues performed a cost-effectiveness analysis comparing IRRT and CRRT in ICU patients with AKI. Despite finding higher up-front costs for CRRT, the total cost over 5 years (including dialysis dependence costs) was lower when CRRT was used as initial treatment compared with IRRT.

Conclusion

CRRT is being used more as an alternative to IRRT in the management of AKI, especially in critically ill patients. It has many applications, and its use can be adapted to fit different situations. Further research is needed, however, to see which patient populations are most likely to benefit from CRRT, to provide definitive criteria for appropriate initiation of treatment, and to determine long-term outcomes related to its use.

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68

Anticoagulation for Continuous Renal Replacement Therapy

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Continuous renal replacement therapy (CRRT) has evolved as the preferred form of dialysis in hemodynamically unstable critically ill patients with acute kidney injury (AKI). It is applied continuously and achieves solute clearance and fluid removal by convection, as in continuous venovenous hemofiltration (CVVH), diffusion, as in continuous venovenous hemodialysis (CVVHD), or a combination of both, as in continuous venovenous hemodiafiltration (CVVHDF). CRRT requires anticoagulation for the prevention of clotting of the extracorporeal circuit. Clotting of the hemofilter reduces total therapy time and leads to decreased dialysis efficacy, blood loss in the extracorporeal circuit, and increased cost because of frequent hemofilter replacements. Hemofilter survival without anticoagulation can be prolonged by facilitating a well-functioning vascular access, maintaining higher blood flow rates, using pre-dilution replacement fluid to reduce the filtration fraction in convective CRRT to less than 20 to 25%, decreasing the blood-air contact in the bubble trap, and assuring prompt reaction to device alarms. Although observational studies have demonstrated that CRRT without anticoagulation is feasible in patients with coagulopathy, most critically ill patients require some form of anticoagulation to achieve adequate dialysis. The ideal anticoagulant for CRRT should have a short half-life and provide optimal antithrombotic activity with low bleeding risk and minimal systemic adverse effects. It should be inexpensive and readily available with simple monitoring methods and have an antidote for easy reversal. This chapter discusses the anticoagulation options available for CRRT with their advantages and disadvantages.

Selecting Anticoagulation Approaches for Continuous Renal Replacement Therapy

The most common anticoagulant options for CRRT include unfractionated heparin (UFH), regional citrate anticoagulation (RCA), and no anticoagulation. Less common anticoagulation options include UFH with protamine reversal, low-molecular-weight heparin (LMWH), thrombin antagonists, and platelet-inhibiting agents. The anticoagulant choice should be determined by the bleeding risk of the patient and the presence of liver failure or heparin-induced thrombocytopenia (HIT) (Table 68.1). The Kidney Disease: Improving Global Outcomes (KDIGO) AKI guidelines recommend using RCA rather than UFH in patients who do not have contraindications to citrate and are with or without increased risk of bleeding. In patients who have contraindications to citrate and are without increased bleeding risk, they recommend using UFH or LMWH rather than other anticoagulants. KDIGO also recommends avoiding regional heparinization during CRRT in patients at increased risk of bleeding. They recommend no anticoagulation in patients with contraindications to citrate use and who are at increased risk of bleeding.

Specific Agents and Anticoagulation Techniques (Table 68.2)

Unfractionated Heparin

In patients at low risk of bleeding, minimal-dose UFH is preferred because it is easy to use, inexpensive, and readily accessible, and has an antidote (protamine). UFH is a mixture of glycosaminoglycans with molecular weights between 5000 and 30,000 Da. It acts by binding to antithrombin III and inhibiting factors IIa and Xa. The larger heparin fragments mainly have anti-IIa activity, while the smaller fragments principally inhibit Xa. An anticoagulant effect from the inhibited Xa can occur in the setting of a normal activated plasma prothrombin time (aPTT) as the smaller fragments have delayed clearance compared to the larger heparin fragments.

A single optimal regimen for UFH administration during CRRT has not been identified. Typical heparin protocols recommend administering UFH into the arterial limb of the dialysis circuit as a bolus of 1000 to 5000 IU (25–30 IU/kg), followed by a continuous infusion of 5 to 15 IU/kg/h. Anticoagulation is monitored by maintaining an aPTT goal

TABLE 68.1 Anticoagulation Choice Based on Clinical Characteristics

Clinical Characteristics	Choice of Agent: No Liver Failure	Choice of Agent: Severe Liver Failure
Low risk of bleeding	UFH, citrate	UFH, No anticoagulation
High risk of bleeding	Citrate	No anticoagulation
Heparin-induced thrombocytopenia	Citrate, argatroban	Bivalirudin

UFH, Unfractionated heparin.

between 45 and 60 seconds (1.5 to 2.0 times normal) or anti-Xa activity between 0.3 and 0.6 IU/mL. However, the optimal target aPTT is not known with certainty, and the therapeutic benefit of preventing clotting in the extracorporeal circuit must be balanced with the risk of systemic bleeding. Disadvantages of UFH include dosing variability arising from complex and unpredictable pharmacokinetics, risk of heparin resistance caused by low patient antithrombin levels, the development of HIT, and the risk of hemorrhage. UFH is contraindicated in patients at high risk of bleeding (e.g., recent surgery, coagulopathy, thrombocytopenia).

Citrate

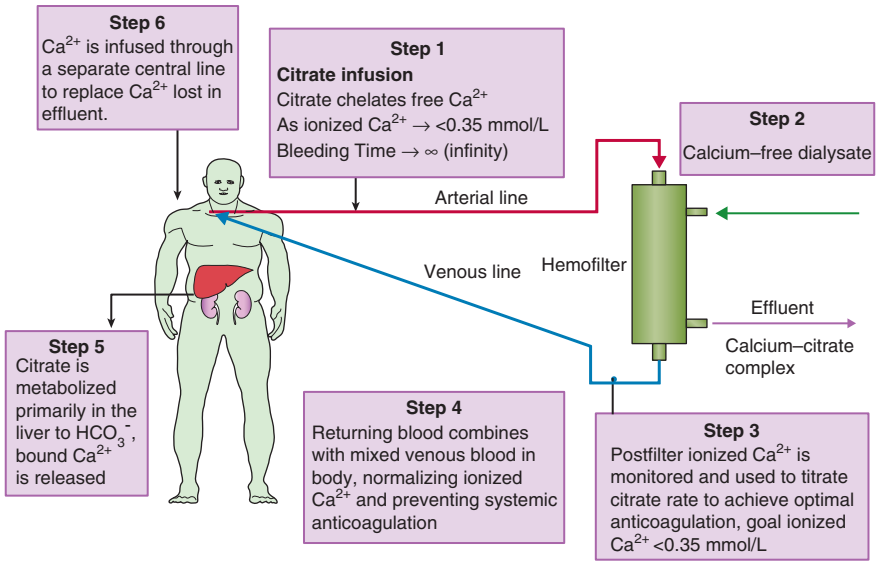
RCA is a widely used alternative to UFH as an anticoagulant for CRRT and limits anticoagulation to the extracorporeal circuit. Advantages of RCA include the avoidance of both systemic anticoagulation and HIT. Furthermore, multiple randomized controlled trials (RCTs) have demonstrated RCA to have a lower risk of bleeding compared with UFH, reduced requirement for transfusion of blood products, and improved hemofilter survival.

Citrate is infused into the blood at the beginning of the CRRT extracorporeal circuit, where it chelates ionized calcium (iCa^{++}) and prevents clotting by making free calcium unavailable to the coagulation cascade (Fig. 68.1). Ionized magnesium is also chelated by citrate but to a lesser extent. Citrate can be administered either as a separate citrate solution or added to a calcium-free pre-dilution replacement fluid. When infused prefilter, citrate is either titrated based on iCa^{++} level or delivered as a fixed ratio between blood and citrate infusions. Optimal regional anticoagulation is

TABLE 68.2 Specific Agents and Anticoagulation Techniques

Agent	Dosing	Monitoring	Comments
Heparin	Bolus: 2000–5000 IU (25–50 IU/kg) Maintenance: 5–15 IU/kg/h	aPTT goal: 45–60 seconds or 1.5 to 2 times normal or anti-Xa activity 0.3–0.6 IU/mL	Contraindicated in high bleeding risk patients Increased risk of HIT
Citrate	Depends on the CRRT operating characteristics and citrate solution composition Infused to achieve a postfilter ionized calcium < 0.35 mmol/L or citrate blood concentration of 3–6 mmol/L	Postfilter ionized calcium, blood electrolytes, and calcium ratio (total calcium to ionized calcium)	Requires IV calcium and frequent electrolyte monitoring Contraindicated in severe liver failure or lactic acidosis
Argatroban	Bolus 100 mcg/kg followed by infusion to achieve a target aPTT of 1.5–3.0 Doses range between 0.7 and 1.7 μg/kg/min	aPTT 1.5–3 times baseline	No antidote Initial dose reduction to 0.5 μg/kg/min in the setting of liver failure
Regional UFH with protamine	UFH is infused prefilter at 1000–1500 U/h Protamine is infused at 10–12 mg/h postfilter to neutralize heparin	Circuit and systemic aPTT	Regional anticoagulation reduces risk of systemic bleeding Technically complicated HIT risk
Enoxaparin Nadroparin Dalteparin	Loading dose 0.1 5 mg/kg and maintenance dose of 0.05 mg/kg/h Loading dose of 15–25 IU/kg followed by a maintenance dose of 5 IU/kg/h	Anti-Xa levels with target levels between 0.25 and 0.35 units/mL	High risk of bleeding Expensive Less reversal with protamine

aPTT, Activated partial thromboplastin time; *CRRT*, continuous kidney replacement therapy; *HIT*, heparin-induced thrombocytopenia; *IV*, intravenous; *UFH*, unfractionated heparin.



• **Fig. 68.1** Schematic representation of regional citrate anticoagulation for continuous kidney replacement therapy.

attained when citrate is titrated to maintain postfilter iCa^{++} concentration in the extracorporeal circuit to less than 0.35 mmol/L, correlating with a citrate blood concentration of 3 to 6 mmol/L. Alternatively, the amount of citrate needed to maintain a concentration of 3 to 4 mmol/L in the blood can be calculated and fixed to the blood flow rate without measurement of post-filter iCa^{++} levels. The majority of the formed calcium–citrate complex is freely filtered across the hemofilter and lost in the effluent. Intravenous calcium chloride or calcium gluconate is infused at an initial rate of 2 to 3 mmol/h to replace the calcium lost in the effluent and titrated to maintain a normal serum iCa^{++} concentration. The remaining calcium–citrate complex that is not filtered is then returned to the patient and metabolized by the liver, kidneys, and skeletal muscles to bicarbonate. Each citrate molecule potentially yields three bicarbonate molecules. Calcium released from the calcium–citrate complex helps restore the serum iCa^{++} levels back to normal.

Because of the lack of universally available commercial citrate formulations specific for CRRT, the citrate solutions used for RCA are either custom made by a pharmacy or available in a concentrated formulation with high sodium content that is not intended for CRRT use. These hypertonic citrate formulations often require compensatory hyponatremic replacement or dialysate solutions with either no or reduced bicarbonate concentrations to prevent the development of metabolic alkalosis. The most commonly used hypertonic citrate formulations in the United States include 2.2% anticoagulant citrate dextrose solution (ACD-A), which contains 224 mmol/L sodium, 74.8 mmol/L citrate, and 38 mmol/L citric acid, and 4% trisodium citrate solution (TSC), which contains 420 mmol/L sodium and 136 mmol/L citrate. Two isotonic dilute citrate formulations specific for CRRT have become commercially available in Europe: Prismocitrate 10/2, which contains 10 mmol/L citrate, 2 mmol/L citric acid, 136 mmol/L sodium, and Prismocitrate 18/0, which contains 18 mmol/L citrate. These isotonic solutions are meant to function as a combined anticoagulant and replacement fluid for convective clearance in CVVH and CVVHDF. Neither of these solutions is available in the United States. Citrate is not currently a Food and Drug Administration–approved anticoagulant for CRRT and therefore is used off label as an anticoagulant for CRRT in the United States.

Electrolyte abnormalities specific to citrate anticoagulation include hypernatremia from the use of hypertonic citrate formulations, metabolic alkalosis, metabolic acidosis, hypomagnesemia, and hypo- or hypercalcemia. Metabolic alkalosis can occur with an excessive citrate load or the administration of exogenous bicarbonate with citrate anticoagulation. Alkalosis risk can be mitigated by decreasing the blood flow and thereby decreasing the amount of citrate needed to maintain a therapeutic level or increasing the effluent flow rate.

Metabolic acidosis can occur when citrate accumulates in patients who cannot metabolize citrate, such as those with liver failure or severe lactic acidosis, resulting in a negative buffer balance. Hallmarks of citrate accumulation include worsening metabolic acidosis, ionized hypocalcemia from unmetabolized calcium–citrate complexes, rising total calcium levels caused by a progressively higher calcium infusion rate, and a disproportionate rise in total systemic calcium to iCa^{++} ratio of greater than 2.5. Severe ionized hypocalcemia can cause hypotension, arrhythmias, and eventually cardiac arrest. Metabolic acidosis can also result if the delivery of citrate is insufficient to buffer the acidosis adequately. This can be corrected by increasing the blood flow or decreasing the effluent rate.

Protocol-driven care with frequent monitoring (every 4–6 hours) of acid-base status and other electrolytes, including ionized calcium, total calcium, phosphorous, and magnesium, is necessary for preventing errors. The need for

monitoring anticoagulation efficacy in the circuit depends on the method of citrate delivery. If the dose of citrate is fixed in relation to the blood flow, frequent monitoring of circuit iCa^{++} levels (i.e., post-filter iCa^{++} levels) is not necessary as long as blood flow is constant. If the citrate dose is not fixed to a constant blood flow rate, post-filter iCa^{++} levels should be measured at least every 6 hours, and the infusion of citrate titrated for an iCa^{++} < 0.35 mmol/L. Once a steady state is reached after 48 to 72 hours and the patient remains stable, monitoring of electrolytes can be decreased to every 12 hours. Citrate should be avoided or used cautiously in patients with severe liver failure or shock liver from hypoperfusion. With adequate monitoring and effective protocols, complications associated with RCA are uncommon.

Regional Unfractionated Heparin with Protamine Reversal

Regional anticoagulation of the circuit is achieved by continuously infusing UFH prefilter via the arterial line and reversing its effects with a constant infusion of protamine administered postfilter into the return line of the extracorporeal circuit. UFH is infused at 1000 to 1500 IU/h prefilter and neutralized with protamine infused at 10 to 12 mg/h infused postfilter. This approach requires measurement of both circuit and patient aPTT for monitoring anticoagulation. This regional anticoagulation lowers the risk of systemic bleeding. The protocol is seldom used because of its technical difficulties and variability in the amount of protamine needed to neutralize heparin. The heparin–protamine complex is taken up by the reticuloendothelial system and released back into circulation after being broken down into heparin and protamine, resulting in heparin rebound and bleeding. Apart from these disadvantages, protamine infusion can cause hypotension, anaphylaxis, cardiac depression, leukopenia, and thrombocytopenia. The efficacy of this modality in prolonging filter lifespan has been variable, although studies have demonstrated its feasibility and safety. Given the risks of HIT from heparin and side effects of protamine, this modality of anticoagulation is not recommended over UFH.

Low-Molecular-Weight Heparin

LMWH acts by inhibiting factor Xa and has a higher anti-Xa/anti IIa activity than UFH because of the lower molecular weight. The pharmacokinetics for LMWH is more predictable, with a reliable anticoagulant response. LMWH is associated with a lower incidence of HIT. Dalteparin, enoxaparin, and nadroparin have been studied among patients receiving CRRT and differ in size, half-life, and activity. Enoxaparin is administered at a loading dose of 0.15 mg/kg and maintained at a dose of 0.05 mg/kg/h. Nadroparin and dalteparin are administered at a loading dose of 15 to 25 IU/kg, followed by a maintenance dose of 5–10 IU/kg/h. Anticoagulation is monitored using anti-Xa levels with target levels between 0.25 and 0.35 units/mL. Higher anti-Xa levels between 0.45 and 0.8 units/mL have been associated with bleeding complications. The disadvantages associated with LMWH include prolonged anticoagulation effect in patients with kidney failure, less effective reversal with protamine because of a stronger anti-Xa effect, requirement of special assays to measure anti-Xa activity, and increased cost compared with UFH. RCTs have shown that fixed-dose LMWHs are as effective but not superior to standard heparin in prolonging circuit life.

Thrombin Antagonists

The most common thrombin antagonists used for anticoagulation of the CRRT circuit in the setting of HIT are argatroban and bivalirudin. Argatroban is metabolized in the liver and has a short half-life of 35 minutes even in patients on chronic dialysis. Anticoagulation is monitored by measuring aPTT levels. Argatroban is administered as a loading dose of 100 μg/kg, followed by a starting infusion of 1 μg/kg/min, or dosing based on the degree of critical illness. The target aPTT is 1.5 to 3.0, and dosing can range between 0.7 and 1.7 μg/kg/min. A formula proposed to determine the argatroban infusion rate in μg/kg/min is as follows: 2.15 − (0.06 × Acute Physiology and Chronic Health Evaluation (APACHE II) score) or 2.06 − (0.03 × Simplified Acute Physiology Score (SAPS) II). A dose reduction is needed in patients with hepatic failure. Disadvantages include bleeding risks and the absence of an antidote. Bivalirudin is used as an alternative to argatroban in patients who have both liver and kidney failure because it has both extrarenal and extrahepatic clearance. It has a short half-life with reversible thrombin binding. One study comparing bivalirudin anticoagulation with heparin anticoagulation in CVVH found longer filter survival times associated with bivalirudin use, which was well tolerated.

Platelet-Inhibiting Agents

Prostacyclin (PGI_2) and its synthetic derivative epoprostenol act by inhibiting platelet aggregation and adhesion. Prostacyclin is infused prefilter at 2 to 8 ng/kg/min. It can be used individually or in combination with low-dose UFH at a rate of 5 to 6 IU/kg/h. Its main disadvantages are its high cost and potential to cause hypotension. There is only limited clinical experience with prostacyclin use with few published reports about its safety and efficacy.

Nafamostat mesylate is another prostacyclin analog that does not cause hypotension and is currently not available in the United States. It is a synthetic serine protease inhibitor that is administered at a dosage of 0.1 mg/kg/h. Anaphylaxis, agranulocytosis, hyperkalemia, and circuit clotting because of decreased protein C activity resulting from increased levels of thrombin–antithrombin III complex and prothrombin activation fragment 1 + 2 are some of the disadvantages limiting its use.

Anticoagulation in Coronavirus Disease 2019 (COVID-19) Infection Patients Requiring CRRT

Severe COVID-19 induces a hypercoagulable state in many critically ill patients, as evidenced by a markedly high rate of clotting of CRRT circuits and higher rates of venous thromboembolism. The pathophysiology of this hypercoagulable state is still unknown, but possible mechanisms include macrophage activation with cytokine release, deficiencies in fibrinolytic pathways, and endothelial injury leading to platelet activation. In this context, RCA has not proven to be nearly as effective in COVID-19 as in other critically ill patients, and therapeutic systemic heparin has been used with some success. Alternatives using direct thrombin inhibitors such as bivalirudin or argatroban can also be considered, although data are limited. Unpublished results from several centers suggest that the combination of RCA and systemic heparin anticoagulation may achieve the best results in these patients. Importantly, some type of anticoagulation should be utilized in COVID-19 patients on CRRT unless there are contraindications, taking into consideration specific logistics available locally at each institution.

Conclusions

There is no consensus on which anticoagulant should be the first choice for all CRRT patients. The choice of anticoagulation primarily depends on patient characteristics such as the risk of bleeding or the presence of other contraindications such as HIT or the presence of liver failure. This choice is also influenced by local expertise, nursing comfort, ease of monitoring, and issues related to pharmacy. Although UFH is most commonly used, citrate anticoagulation is gaining wider acceptance as an alternative anticoagulation approach with the evolution of simplified and safer protocols.

Recommended Reading

Bai M, Zhou M, He L, et al. Citrate versus heparin anticoagulation for continuous kidney replacement therapy: an updated meta-analysis of RCTs. *Intensive Care Med.* 2015;41:2098.

This meta-analysis of RCTs assessing the effect of citrate versus heparin anticoagulation for CRRT therapy reported that regional citrate should be considered as a better anticoagulation method than heparin for CRRT in critically ill patients without any contraindication due to lower risk of circuit loss, filter failure, bleeding, and HIT.

Gattas DJ, Rajbhandari D, Bradford C, et al. A randomized controlled trial of regional citrate versus regional heparin anticoagulation for continuous kidney replacement therapy in critically ill adults. *Crit Care Med.* 2015;43:1622.

The authors in this multicenter, parallel group RCT in critically ill adult patients requiring CRRT reported that RCA prolongs CRRT circuit life and is associated with fewer adverse events when compared with regional heparin and protamine anticoagulation.

Link A, Girndt M, Selejan S, Mathes A, Bohm M, Rensing H. Argatroban for anticoagulation in continuous kidney replacement therapy. *Crit Care Med.* 2009;37(1):105–110.

This prospective dose finding study among medical and surgical patients with acute or histories of HIT type II and acute kidney failure with necessity for CRRT reported that critical illness scores (APACHE II, SAPS II) or ICG-PDR can help in predicting the required argatroban maintenance dose for anticoagulation.

Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl.* 2012;2:1–138.

Clinical practice guidelines for AKI management containing evidence-based recommendations for anticoagulation use in CRRT to assist in clinical decision making.

Morabito S, Pistolesi V, Tritapepe L, Fiaccadori E. Regional citrate anticoagulation for RRTs in critically ill patients with AKI. *Clin J Am Soc Nephrol.* 2014;9(12):2173–2188.

Review article providing a critical overview of RCA in patients undergoing kidney replacement therapy (RRT) for AKI. Discusses the practical application of RCA for various RRT modalities. Provides specific treatment protocols and also discusses future perspectives for simplification of RCA protocols.

Schneider AG, Journois D, Rimmelé T. Complications of regional citrate anticoagulation: accumulation or overload? *Crit Care.* 2017;21(1):281.

This review article provides clarifications on RCA-associated acid-base disturbances and their management at the bedside with particular emphasis to clearly distinguish citrate accumulation and net citrate overload.

Slowinski T, Morgera S, Joannidis M, et al. Safety and efficacy of regional citrate anticoagulation in continuous venovenous hemodialysis in the presence of liver failure: the Liver Citrate Anticoagulation Threshold (L-CAT) observational study. *Crit Care.* 2015;19:349.

This multicenter, prospective, observational study looked at safety and efficacy of RCA in patients with liver failure requiring CVVHD. The authors report that RCA can be safely used in patients with liver failure with excellent filter patency with the technique.

Stucker F, Ponte B, Tataw J, et al. Efficacy and safety of citrate-based anticoagulation compared to heparin in patients with acute kidney injury requiring continuous kidney replacement therapy: a randomized controlled trial. *Crit Care.* 2015;19:91.

Authors report the results of an RCT with patients requiring CRRT to determine whether RCA using a balanced predilution replacement fluid is more effective than heparin in terms of kidney replacement delivered dose and safety profile. Results indicate that RCA is superior to heparin-based anticoagulation in terms of delivered dose and filter life span and is a safe and feasible method.

Tsujimoto H, Tsujimoto Y, Nakata Y, et al. Pharmacological interventions for preventing clotting of extracorporeal circuits during continuous kidney replacement therapy. *Cochrane Database Syst Rev.* 2020;3, CD012467.

This Cochrane database review of RCT and quasi-RCTs assessed the benefits and harms of pharmacological interventions for preventing clotting in the extracorporeal circuits during CRRT. The authors found that available evidence does not support the overall superiority of any anticoagulant to another but did report that citrate probably reduces major bleeding and probably has little or no effect on preventing clotting or death at 28 days when compared to UFH.

Tang IY, Cox DS, Patel K, et al. Argatroban and kidney replacement therapy in patients with heparin-induced thrombocytopenia. *Ann Pharmacother.* 2005;39(2):231–236.

This prospective study evaluated the pharmacokinetics, pharmacodynamics, and safety of argatroban during RRT in hospitalized patients with or at risk for HIT. It concluded that argatroban is an effective alternative anticoagulation method in patients with or at risk for HIT during RRT.

Tolwani A, Wille KM. Advances in continuous kidney replacement therapy: citrate anticoagulation update. *Blood Purif.* 2012;34(2):88–93.

This article summarizes the characteristics of citrate as an anticoagulant and provides an update on the use of citrate in CRRT.

Tovey L, Dickie H, Gangi S, et al. Beyond the randomized clinical trial: citrate for continuous kidney replacement therapy in clinical practice. *Nephron Clin Pract.* 2013;124(1-2):119–123.

This study retrospectively analyzed data on circuit patency of all CRRT circuits used in a single center and concluded that regional anticoagulation with citrate was associated with significantly better circuit patency than heparin or epoprostenol.

69

Treatment of Poisoning with Extracorporeal Methods

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More than 2 million poisonings were reported to the American Association of Poison Control Centers in 2021. Outcomes are generally favorable, and supportive measures alone are sufficient to manage the majority of poisonings. In selected situations, gastrointestinal decontamination, timely administration of antidotes, and elimination enhancement treatments may be administered to prevent or reverse toxicity. Urine alkalinization was reported in 0.6% of cases, and multiple-dose activated charcoal was used in 0.05% and extracorporeal treatments (ECTRs) such as hemodialysis (HD) in 0.1% of all cases. However, the number of poisoned patients being treated with HD and related ECTRs is increasing each year, and the types of poisonings being treated are also changing with time. This prompts review and consideration of the indications for ECTRs and operational characteristics that maximize the effect of such treatments.

General Overview of the Treatment of the Poisoned Patient

Background

The range of drugs, chemicals, and natural toxins that can induce poisoning is vast, as are their manifestations. Acute poisoning may follow intentional self-poisoning or a single prescribing or dosing error; chronic poisoning most commonly follows a prescribing or dosing error leading to a drug–drug interaction or a drug–disease interaction due to intercurrent conditions, such as impaired kidney function.

Initial Treatment

The initial steps to the management of all poisoned patients are resuscitation, risk assessment, close observation, and supportive care. Careful attention to these basic critical care skills is central to management of any poisoned patient, in view of the potential for multisystem manifestations, especially when the incriminating poison and/or exposure are unknown. When the poison exposure is confirmed, toxicity should be anticipated so that necessary interventions can be instituted. Patients who are clinically unstable, or may become so, should be managed in a critical care environment. Early intubation is commonly required for airway protection and is often performed preemptively in exposures that can develop severe toxicity. Hypotension may be cardiogenic, hypovolemic, or distributive in nature, depending on the poison, and resuscitation, inotrope, or vasopressor support is guided by the specific etiology. Supportive care may also include correction of poison-induced dysrhythmias, hypothermia or hyperthermia, and seizures according to current recommendations (reviewed elsewhere).

Risk Assessment

After resuscitation, a careful risk assessment is required to guide further treatment. The risk assessment is a detailed cognitive process that incorporates consideration of the exposure (type and amount), time since the exposure, likely clinical manifestations, resources required such as critical care support, antidotes, and access to ECTRs in a clinically reasonable time frame. This may be supported by blood tests, such as the anion gap, an osmol gap, or a poison concentration. The risk assessment guides the duration of observation, place for admission, and treatments required. For example, it may prompt transfer to another institution for the purpose of treatment with ECTR. Prompt communication with a regional poison center will assist with the risk assessment and offer valuable expertise on management issues.

Decontamination

Decontamination is defined as the prevention of absorption of a poison. This may be dermal (e.g., chemical spills), ocular, or gastrointestinal. Various therapeutic options are available for gastrointestinal decontamination. Activated charcoal 1 to 2 g/kg enterally is usually the preferred agent for most poisons, but its effect is limited to use with organic nonpolar

poisons such as metals and alcohols. Its main beneficial effect is within 1 hour of ingestion, although delayed administration may have a role with massive exposures, sustained-release preparations, or poisonings associated with delayed gut transit (e.g., opioid agonists or anticholinergic drugs).

Whole-bowel irrigation using polyethylene glycol 1 to 2 L/h enterally is sometimes used in the treatment of poisonings with sustained-release medications, massive exposures, or those that are not adsorbed to charcoal, such as metals including lithium, iron, and lead. Gastric lavage, forced emesis, and other cathartics have a minimal role in the majority of poisonings.

Antidotes

Antidotes are drugs that can reverse or reduce toxicity, such as naloxone for opioid poisoning, ethanol or fomepizole for toxic alcohols, oxygen for carbon monoxide, chelators for certain metals, sodium bicarbonate for sodium channel blocking agents, methylene blue for methemoglobinemia, and others.

In the event that an ECTR is also required for the treatment of such a poisoning, it is necessary to ascertain whether the ECTR will remove the antidote. If the antidote dosage is not increased accordingly, this may result in subtherapeutic concentrations; this has been demonstrated for *N*-acetylcysteine, ethanol, and fomepizole.

Enhanced Elimination

A final but important consideration in the medical treatment of poisoning is the potential benefit of enhanced elimination. Here, treatments increase the total clearance of the poison, with the aim of shortening poisoning duration and severity.

Multiple doses of activated charcoal (MDACs) are recommended to enhance the elimination of a number of poisons, including carbamazepine, dapsone, quinine, phenobarbital, and theophylline. MDAC may also facilitate elimination of cardiac glycosides, phenytoin, aspirin, colchicine, and amatoxin. The mechanism of action is not completely understood for each indication but may relate to interruption of enterohepatic circulation, enteral dialysis, or interfering with a prolonged absorption phase.

Urinary alkalinization with sodium bicarbonate can enhance the elimination or reduce nephrotoxicity of some poisons. Increasing urine pH either promotes solubility of the poison or, in the case of weak acids (i.e., with a dissociation constant, pKa, lower than the urinary physiologic pH), increases the proportion of poison that is ionized, which enhances urinary elimination. Clinical applications of urine alkalinization include salicylate, chlorophenoxy herbicides (e.g., 2-methyl-4-chlorophenoxyacetic acid [MCPA], 2,4-dichlorophenoxyacetic acid [2,4-D]), and to a lesser extent for methotrexate, myoglobin, and fluoride. It has also been used in phenobarbital poisoning, but the effect is less than that of MDAC, so here it is only used if MDAC cannot be given (e.g., because of ileus). Potential complications associated with urine alkalinization are alkalemia, hypokalemia, hypocalcemia, hypernatremia, and volume overload. In fact, alkaline urine is achieved only in the presence of normokalemia.

ECTRs can significantly enhance the elimination of a range of poisons (as well as their metabolites).

Characteristics of a Potentially Dialyzable Toxin

In the context of treating poisoning, it is necessary to understand the key principles that promote solute removal by ECTR. This reflects the properties of the poison, and these are defined by its physicochemical and pharmacokinetic parameters. Factors governing poison removal are the same as those for uremic toxins.

Physicochemical

Smaller-sized molecules are more effectively removed by ECTRs. Previous filter technology limited removal of poisons to those that were less than approximately 500 Da, but current membranes allow removal of poisons with molecular weight up to 10,000 Da by HD and 50,000 Da by hemofiltration (HF). Highly protein-bound poisons cannot cross most filters or dialyzers because the size of the complex exceeds the cutoff of most filters. In contrast, protein binding is less of a barrier to achieving a high clearance if hemoperfusion (HP) cartridges are used. A particular consideration in poisoning is that protein binding can become saturated at very high concentrations (for example, salicylate and valproic acid), resulting in a relatively higher concentration that is unbound to plasma proteins and therefore crosses HD membranes to a more significant extent than that noted at lower concentrations.

Pharmacokinetics

ECTRs are potentially useful for enhancing the elimination of poison if they provide a significant increase in total clearance relative to endogenous clearance. The larger the proportion that extracorporeal clearance increases total clearance, the more useful the procedure. Endogenous clearance can decrease when organ injury impacts the route of elimination of the poison. As an illustration, metformin endogenous clearance is 600 mL/min in patients with intact kidney function and decreases to 0 mL/min in anuric patients with acute kidney injury (AKI), whereas extracorporeal metformin clearance can reach 250 mL/min; ECTR would therefore provide more relative benefit in the latter situation. Endogenous clearance may also vary when a nutrient is a cofactor in the catabolism of the poison (e.g., folate or folinic acid and methanol). Additionally, because ECTRs remove poison directly from the intravascular space, poisons that exhibit a low volume of distribution (< 1–2 L/kg) are best suited for extracorporeal removal. Specific guidance regarding what constitutes a potentially significant benefit from an

ECTR in a poisoning depends on the specific poison and exposure, time since presentation, mechanism of toxicity, and relative impact of extracorporeal clearance in relation to total body clearance of the poison.

Choice of Extracorporeal Treatment

Although the favored extracorporeal modalities for the correction of uremia are intermittent HD, peritoneal dialysis (PD), or continuous renal replacement therapy (CRRT), several other ECTRs have been advocated for enhancing the elimination of a poison (Table 69.1). Ultimately, the choice of which ECTR to use depends on the poison's physicochemical characteristics, the patient's condition, comorbid conditions, and local availability of ECTRs.

Hemodialysis

During HD, poison diffuses from the blood into a countercurrent dialysate, both of which are separated by a semipermeable membrane (Table 69.2). Characteristics of poison removal by HD include a low molecular size (< 10,000 Da), a low volume of distribution, and a low protein binding (< 80%).

HD has several distinct advantages over other ECTRs in the management of acute poisonings: it is more widely available and less expensive than other techniques and HD also rapidly corrects conditions associated with certain poisonings such as AKI, volume overload, acid-base abnormalities,

TABLE 69.2 Factors That Optimize Poison Clearance During Hemodialysis

Larger surface area of dialysis membrane
High-flux dialyzer
High blood and dialysate flow
Increased ultrafiltration rate (with replacement solution)
Increased time on dialysis
A vascular site that has less recirculation
Two dialyzers in series
Two distinct extracorporeal circuits

TABLE 69.1 Summary of Extracorporeal Treatments

Technique	Process	Molecular Cutoff (Da)	Protein Binding Cutoff	Maximal Clearance	Relative Cost	Complications	Comments
Hemodialysis	Diffusion	< 10,000	< 80%	400 mL/min	+	+	Also corrects of uremia and acid–base/electrolyte disorders
Hemoperfusion	Adsorption	< 50,000	< 95%	350 mL/min	++	+++	Saturation of cartridge which reduces drug clearance
Hemofiltration	Convection	< 50,000	< 80%	400 mL/min	++	+	Also corrects of uremia and acid–base/electrolyte disorders
Therapeutic plasma exchange	Centrifugation, separation, filtration	< 1,000,000	None	50 mL/min	+++	+++	
Albumin dialysis	Diffusion, adsorption	< 300,000	< 95%	400 mL/min	++++	++	Liver replacement support
Exchange transfusion	Centrifugation, separation, filtration	None	None	10 mL/min	++	++	Simpler in neonates Correction of hemolysis
Peritoneal dialysis	Diffusion	< 5000	< 80%	15 mL/min	++	++	

All extracorporeal treatments in the table are less useful for poisons that have a high volume of distribution or a high endogenous clearance.

and electrolyte disturbances. HD is more widely available, less costly, and less often fraught with complications compared with HP or plasma exchange, for example.

Hemoperfusion

During HP, blood passes over a charcoal-coated column (resins are no longer available in the United States) on to which the poison is adsorbed. HP is better suited for protein-bound poisons than HD; HP cannot adsorb alcohols and most metals. Charcoal cartridges are seldom available in dialysis units and are approximately 10 times more expensive than a high-flux dialyzer. Cartridges can also nonselectively adsorb glucose, platelets, calcium, and white blood cells, which may have clinical repercussions in poisoning situations. This nonselective binding of plasma components contributes to early saturation of the cartridge, requiring it to be replaced every 2 to 3 hours to maintain high clearances. HP can also cause hemolysis; the circuit requires more systemic anticoagulation than with HD to prevent this, and the blood flow must be limited to less than 350 mL/min.

The advantages of HP have been questioned, particularly in recent years, due to improved poison clearances achieved with high-efficiency dialyzers. In addition, HP does not allow for correction of uremia and electrolyte or acid-base disturbances. For these reasons, HD is generally preferred in almost all settings when HP is considered indicated. Experience with the CytoSorb® adsorber, which can adsorb xenobiotics up to 60,000 Da is limited.

Hemofiltration

During HF, solute and solvent are removed by solute drag, a process known as convection, and replaced by a physiologic solution (see Chapter 12). Poisons that are eliminated by HD will also be eliminated by HF. Although even high-flux dialyzers do not allow passage of poisons that are larger than 10,000 Da, hemofilters have a cutoff of approximately 50,000 Da. This has relatively little clinical relevance in toxicology, considering that the overwhelming proportion of drugs and poisons have a molecular size below 1000 Da. However, some data suggest that myoglobin may be cleared by HF, which is notable because rhabdomyolysis occurs with some poisonings.

Continuous Renal Replacement Therapy

Continuous techniques (see Chapter 67) are a popular choice for the management of AKI in the critical care setting. These modalities are attractive because net fluid removal can be extended over 24 hours instead of the usual 4 hours for HD, thereby reducing the risk of hypotension. However, this advantage appears marginal in most poisonings in which fluid overload is rarely present. Another popular argument for continuous techniques is the avoidance of the usual increase in poison blood concentration after ECTR ("rebound"). When rebound is caused by redistribution of poison from intracellular or extravascular compartments to the plasma, this surge in plasma concentration may be balanced by a decrease in poison concentration away from its toxic compartment when this compartment is located extravascularly. It is therefore disputable if the rebound in this scenario would be clinically detrimental. If concerning, for example, with dabigatran in which the rebound may increase bleeding risk, the rebound can be minimized by a prolonged dialysis session, by a switch to CRRT after HD, or with a subsequent HD session. Although the postulated advantages for CRRT may be disputed, the major downside is lesser poison clearance by virtue of lower blood and effluent flows. This underlies present recommendations supporting a preference for high-efficiency intermittent ECTR unless local factors prevent the use of intermittent high-efficiency dialysis.

Peritoneal Dialysis

The role of PD in acute poisoning is limited because more efficient techniques offer poison clearances that are more than 10-fold greater than those obtained with PD. PD should be considered only in severe poisonings involving infants or when other modalities are unavailable. In these cases, frequent dialysate exchanges with large volumes will maximize clearance.

Therapeutic Plasma Exchange

Therapeutic plasma exchange (TPE) is a process by which plasma is separated from blood cells, discarded, and then replaced by either albumin or fresh-frozen plasma. Plasma clearance during plasma exchange is usually limited to 50 mL/min. The role of TPE in the treatment of acute poisoning is not well defined, but this method should be considered only for poisons that are highly protein bound (> 95%) or for poisons with a molecular size over the cutoffs treatable with HF or HP (> 50,000 Da), such as monoclonal antibodies. Adverse outcomes from plasma exchange involve complications associated with placement of the vascular access, bleeding, hypocalcemia, and hypersensitivity reactions to the replacement plasma proteins.

Exchange Transfusion

Exchange transfusion (ET) is a treatment in which whole blood is removed and replaced with transfused blood products. Poison clearance is very limited during ET (10–15 mL/min); however, ET does not require a central venous access and sophisticated machinery, so it may be considered in settings where HD is not available, especially in infants, for whom ET is easier to perform than other treatments.

Liver Support Devices (Albumin Dialysis)

Liver support devices (LSDs) were developed to support liver function in the context of fulminant hepatic failure or cirrhosis. These devices theoretically remove albumin-bound

toxins and xenobiotics better than the more commonly used diffusive and convective techniques. However, preliminary clearance data do not show any superiority for LSDs in poisonings with theophylline, valproic acid, or phenytoin. Because of their very limited availability and high cost (>$10,000 per treatment), they are usually reserved as a temporary bridge to liver transplantation or spontaneous remission rather than for their capacity to eliminate poison. Several reports describe the use of LSDs in toxin-induced hepatotoxicity, including *Amanita* mushroom and acetaminophen, although the practical applicability of these techniques remains uncertain.

Technical Considerations

Poisoned patients have clinical characteristics that differ from patients with either AKI or end-stage kidney disease. The application of any ECTR should be determined on a case-by-case basis reflecting these differences.

Vascular access: A double-lumen central catheter is required for administering most forms of ECTRs. The femoral site is often preferred for its simplicity but has more recirculation than subclavian or jugular sites.

Choice of hemodialyzer, filter, and adsorber: The dialyzer or hemofilter must have a molecular size cutoff larger than that of the poison, and filters used routinely in dialysis facilities are acceptable in almost all cases. High-efficiency dialyzers with larger surface areas will improve clearance of low-molecular-size poisons, which includes almost all drugs of relevance. With respect to HP, the only column available in the United States is the Gambro Adsorba 300c, a coated activated charcoal cartridge.

Anticoagulation: Anticoagulation of the dialysis circuit should be considered to prevent clotting and maintain patency of the circuit. In patients at high risk of bleeding, saline flushes can be used instead of anticoagulation. For HP, heparin is also used to reduce the risk of hemolysis and is usually required in larger doses than required for HD.

Blood, dialysate, and effluent flow: Because the risk of dialysis disequilibrium is considered low in the context of acute poisoning, except perhaps in massive methanol or ethylene glycol poisoning because of the risk of fluid shifts due to hyperosmolarity, blood and effluent flow should be maximized to optimize clearance. Most poisoned patients are not volume overloaded (volume depletion is more common), so net ultrafiltration is usually not required.

Dialysate composition: As mentioned, poisoned patients may not share the same metabolic characteristics as those with kidney failure. Bicarbonate, potassium, calcium, and magnesium need to be adjusted in the dialysate bath (or replacement fluid) to meet the requirements of the poisoned patient. Phosphate may also be added to the bath to avoid hypophosphatemia with prolonged treatments.

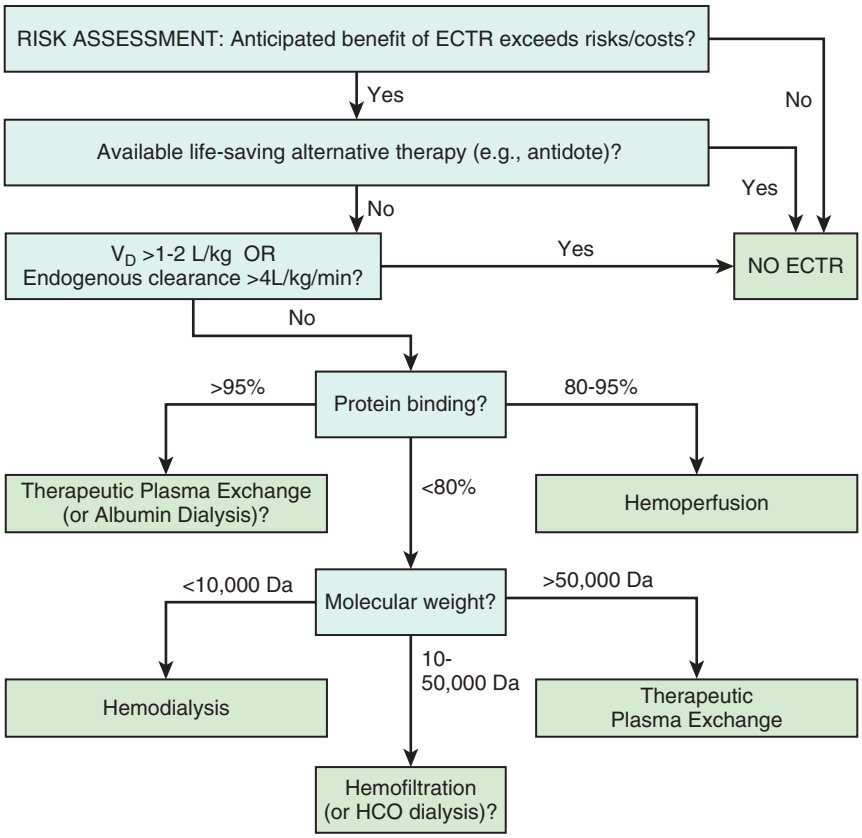
Duration of extracorporeal treatment: A single 6-hour HD will usually suffice to substantially lower blood levels of most xenobiotics, although the length of the procedure will ultimately depend on the efficacy of the procedure used and the body burden of poison to remove. Sequential HD followed by CRRT is used in some cases to minimize the rebound in drug concentrations.

Patient disposition: Many severely poisoned patients die before initiation of dialysis. If the risk assessment of a suspected or known toxic exposure suggests that a patient may benefit from dialysis, prompt communication with a dialysis facility and consideration of preemptive transfer to one may be required, even if the patient does not yet meet criteria for blood purification. Because significant delays may occur between a decision is made to perform ECTR and the time when it is initiated, a dialysis nurse should be rapidly contacted and a temporary dialysis catheter installed as early as possible. Logistics and clinical status may require transfer of the patient to the intensive care unit (ICU). After ECTR, serial poison concentrations and clinical status should be monitored for a period long enough to account for redistribution or ongoing absorption (≈12–24 hours). The catheter should remain in place until the physician is convinced that additional sessions are unnecessary.

General Principles Regarding the Use of Extracorporeal Treatment in the Management of Poisoning

The decision to initiate any form of blood purification must take into account the patient's clinical status, the benefit expected from the ECTR, and poison-related factors. Indications for ECTR are summarized in Fig. 69.1 and include the following (all must be present):

1. **The ECTR will remove the poison to a significant extent:** This has been discussed earlier. Specifically, the poison is dialyzable if (a) it readily passes through the extracorporeal membrane, (b) it has a low volume of distribution, and (c) clearance by ECTR represents a significant portion of total body clearance. The extent of removal reflects endogenous clearance (e.g., impaired kidney function) and ECTR-related factors such as membrane type, membrane surface area, and blood and dialysate flow rates (see Table 69.1).
2. **The patient is at risk of severe poisoning.** ECTR should be considered when life-threatening conditions resulting from poisoning are either present or are expected to occur. Clinical signs include neurotoxicity (e.g., repeated seizures, coma), respiratory depression, cardiotoxicity (major dysrhythmias), as well as severe metabolic disequilibria, in particular acidosis. Less commonly, the onset of severe clinical effects may be delayed (e.g., methanol, paraquat, valproate), so monitoring drug concentrations aids prognostication and guides the use of *prophylactic* ECTR (i.e., before the appearance of such toxicity).



• **Fig. 69.1** Stepwise approach to extracorporeal treatment in poisoning contexts. *ECTR*, Extracorporeal treatment; *HCO*, bicarbonate; V_D, volume of distribution. (Reproduced with permission from Ghannoum M, Roberts DM, Hoffman RS, et al. A stepwise approach for the management of poisoning with extracorporeal treatments. *Semin Dial.* 2014;27(4):362–370.)

3. **Absence of equally effective alternative treatment(s).** ECTR is not indicated when outcomes of a specific poisoning are not improved compared to that by supportive measures or by the administration of an antidote. However, there are certain cases when it may shorten the duration of admission, which is economically favorable, for example, uncomplicated massive toxic alcohol poisonings.

It is necessary for the clinician to balance the benefits expected from ECTR against the costs and complications of the procedure on a case-by-case basis: Benefits would far outweigh risks when the poison's exposure is associated with short-term mortality (e.g., salicylates) or irreversible tissue damage (e.g., blindness from methanol). The benefits from ECTR in these circumstances would largely outweigh any risk associated with the procedure.

ECTR might also be indicated if the poison predisposes to prolonged hospital admission and associated costs. For example, phenobarbital poisoning may require protracted mechanical ventilation in the ICU. Alternatively, in the case of early methanol poisoning treated with fomepizole, ECTR is not required to reduce toxicity, but ECTR can reduce the length of hospitalization, complications of ethanol, and cost of fomepizole administration.

The risks of acute ECTR include not only catheter-related adverse events but also potential removal of antidotes and other therapeutic drugs, causing a loss of therapeutic effect. ECTR may also precipitate withdrawal symptoms if drug levels fall below the therapeutic range in patients who are physically dependent to that drug, for example, phenobarbital or baclofen. The cost of a single dialysis session is usually a fraction of the total cost of one day's admission in the ICU.

Specific Indications for Poisons That Are Currently Considered Dialyzable

Incorporating the various principles stated earlier, specific indications for poisons that are potentially amenable to enhanced elimination by ECTR are presented in Table 69.3. This reflects recent consensus statements by the Extracorporeal Treatments in Poisoning Workshop (EXTRIP) workgroup (http://www.extrip-workgroup.org), and it is an area of ongoing research and review. Research has reported benefits when other drugs and poisons have been treated with ECTR, including poisoning from paraquat, baclofen, pregabalin, and dabigatran, for which ECTR may also be considered in certain circumstances. In contrast, there are no current indications for ECTR for tricyclic antidepressants, digoxin, benzodiazepines, calcium channel blockers, and antimalarials, and the indications for phenytoin poisoning remain debated.

TABLE 69.3 **Summary of Recommendations for ECTR in Poisons Amenable to Extracorporeal Removal**

Poison	Indications		Choice of ECTR	Cessation of ECTR When	Other Considerations
	Poison Concentration	Clinical and Laboratory			
Acetaminophen	>1000 mg/L (6620 μmol/L)	Metabolic acidosis, coma	HD > CRRT	Clinical improvement	Dose of NAC should be at least doubled.
Barbiturates (long acting)	Increasing or persisting (not specified)	Coma, mechanical ventilation, shock	HD > HP/CRRT	Clinical improvement	Coadminister MDAC.
Carbamazepine	Increasing or persisting (not specified)	Refractory seizures, life-threatening dysrhythmias, prolonged coma, respiratory depression requiring mechanical ventilation, toxicity despite MDAC	HD > CRRT/HP	Clinical improvement *or* carbamazepine <10 mg/L (42 μmol/L)	MDAC therapy should be continued.
Dabigatran	Increasing or persisting (not specified)	Active bleeding and abnormal coagulation parameters	HD > CRRT	Significant improvement of coagulation parameters and bleeding cessation	Consider use of idarucizumab, closely monitor for recurrence of poisoning after ECTR.
Lithium	>5.0 mEq/L	Decreased LOC, seizures, dysrhythmias, impaired kidney function	HD > CRRT	Clinical improvement *or* Li <1.0 mEq/L	Consider CRRT after HD.
Ethylene glycol	>310 mg/dL (50 mmol/L; if antidote used)	Shock, coma, seizures, anion gap >24 mmol/L, AKI	HD > CRRT	Clinical improvement AND ethylene glycol <10 mg/dL (1.6 mmol/L)	ECTR may not be required if normal kidney function. The dose of antidotes (ethanol or fomepizole) must be adjusted during ECTR.
Metformin	Not specified	Shock, failure of standard supportive measures, decreased LOC, lactate >20 mmol/L, pH <7.0	HD > CRRT	Lactate <3 mmol/L *and* pH >7.35	Repeat sessions using HD or CRRT. Closely monitor lactate and pH for additional ECTR courses.
Methanol	>70 mg/dL (21.8 mmol/L; if fomepizole used) >60 mg/dL (18.7 mmol/L; if ethanol used) >50 mg/dL (15.6 mmol/L; if no antidote used)	Coma, seizures, new vision deficits, pH ≤7.15, anion gap >24 mmol/L	HD > CRRT	Clinical improvement *and* methanol <20 mg/dL (6.2 mmol/L)	The dose of antidotes (ethanol or fomepizole) must be adjusted during ECTR. Folic acid should be continued during ECTR.
Salicylates	>100 mg/dL (7.2 mmol/L)	Altered mental status, ARDS, impaired renal function, pH ≤7.20	HD > HP > CRRT	Clinical improvement AND salicylate <20 mg/dL (1.4 mmol/L)	ET may be used in children/coadminister MDAC.
Theophylline	>100 mg/L (555 mmol/L; acute exposure) >60 mg/L (333 mmol/L; chronic poisoning)	Seizures, life-threatening dysrhythmias, shock, clinical deterioration despite optimal care, GI decontamination cannot be administered	HD > HP > CRRT	Clinical improvement *or* theophylline <15 mg/L (83 mmol/L)	Coadminister MDAC.
Valproic acid	>1300 mg/L (9000 μmol/L)	Cerebral edema, coma, shock, acute hyperammonemia, pH ≤7.10, respiratory depression	HD > CRRT/HP	Clinical improvement or VPA <100 mg/L (700 μmol/L)	

AKI, Acute kidney injury; *ARDS*, acute respiratory distress syndrome; *CRRT*, continuous renal replacement therapy; *ECTR*, extracorporeal treatment; *ET*, exchange transfusion; *GI*, gastrointestinal; *HD*, intermittent hemodialysis; *HP*, hemoperfusion; *LOC*, level of consciousness; *MDAC*, multiple doses of activated charcoal; *NAC*, *N*-acetylcysteine; *VPA*, valproic acid.

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PART II

Dialysis Therapy for Children

70

Vascular Access and Peritoneal Dialysis Catheter Placement in Children

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DIALYSIS ACCESS IN THE PEDIATRIC ESRD PATIENT

Vascular Access in Children

Introduction

Renal transplantation is the most common renal replacement modality for prevalent children with end-stage renal disease (ESRD). However, hemodialysis (HD) continues to be the most common initial treatment. Of 1319 incident children with ESRD in 2017, 51.3% began treatment with HD. Because of their young age, children with ESRD will require decades of renal replacement therapy and will need HD at some point in their lives. Worldwide, most prevalent children on HD are dialyzed with a central venous catheter (CVC), whereas only about 25% are dialyzed with an arteriovenous fistula (AVF). This preference for CVC for long-term HD continues in spite of international efforts and guidelines emphasizing the clinical importance of creating a permanent vascular access, AVF or arteriovenous graft (AVG), for long-term HD in children.

CVCs offer the benefit of immediate and painless access and are best suited for acute HD. However, when used long-term, CVCs have a high risk of infection and malfunction and place the child at significant risk for central venous stenosis and thrombosis. Recurrent hospitalizations and procedures to replace CVCs not only increase health care costs but also increase missed school days in the life of a developing child, thereby impairing cognitive and social development. Expected short time to transplant in children is another reason CVCs are favored. However, most children on HD spend at least 1 year on dialysis before receiving a renal transplant.

Arteriovenous Fistulae

AVFs are the ideal vascular access for chronic HD as they allow for high blood flow rates resulting in efficient and effective dialysis delivery. They also have the best long-term survival and the lowest rate of complications and hospitalizations. Children dialyzed with an AVF have higher Kt/V, higher albumin levels, and a higher mean hemoglobin concentration and require lower doses of erythropoietin compared to children dialyzed with a CVC. In addition to these benefits, children with an AVF can bathe and swim without restrictions. Disadvantages include needling pain and physical changes in the appearance of the arm.

Although the Fistula First Initiative (FFI), sponsored by the Centers for Medicare and Medicaid Services, did not include pediatric patients, an international pediatric FFI was introduced in 2008 to increase AVF creation in children. Undoubtedly, AVF creation in small patients can be challenging, particularly in children with early onset of chronic kidney disease (CKD), history of multiple hospitalizations, and central line placements with resulting central venous stenosis. Over the years, improved surgical expertise, the use of microsurgery techniques in select centers, and the institution of multidisciplinary vascular teams have resulted in improved success rates of AVF creation and use in many centers around the world. Patency rates are now similar to those reported in adults, even for small children.

Preparation

Vein preservation is of particular importance for future AVF creation. Upon diagnosis of CKD in a child, patients and families should be educated on the importance of protecting veins, especially in the nondominant arm. Venipunctures for blood draws and intravenous lines should be performed at distal sites of the dominant arm whenever possible.

Educating the patient and family will empower them to best defend their "venous capital."

Location

In general, "distal before proximal" and "autogenous before prosthetic" principles should be followed when planning an AVF. The nondominant arm is the preferred limb. If vessels on the nondominant arm are not adequate, the dominant arm is then preferred over the lower limb. A wrist AVF (radiocephalic) remains the first choice for chronic HD in children. The surgery involves the cephalic vein, which is anastomosed to the radial artery in an end-to-side fashion. This AVF allows for preservation of more proximal vessels for future access, and it has high long-term patency. The disadvantages include high primary failure rates when microsurgery is not used and a long maturation time in young children. The high primary failure rates in small children are attributed to small vessel size, vascular spasm, and poor venous outflow.

If a radiocephalic AVF is not possible, or primary failure occurs, the brachial artery can be used in the creation of a brachio-cephalic AVF in the elbow as the next preferred location. A brachio-basilic AVF is another option on the upper arm. Two-stage basilic vein transposition allows for maturation of small veins, which can offer a superior alternative in small children. The basilic vein, located deep in the upper arm, is usually protected from the repeated trauma of previous venipunctures and may be of particular use in children who have small vessels and are not good candidates for a more distal AVF. The arterialized vein, once it has reached a diameter of 6 mm, is moved up to a more superficial position in a second-stage procedure to allow for easier cannulation. This type of AVF has been reported to have high immediate and long-term patency rates. Another alternative is the use of the proximal radial artery. Construction of this AVF involves disruption of venous valves to achieve bidirectional AVF flow. The vein used depends on the patient's anatomy and can include the median antebrachial, median cephalic, median cubital, or deep communicating vein. This type of AVF has a lower risk of steal phenomena than brachial artery fistulae and has been successfully used in children with high patency rates.

Following the "autogenous before prosthetic" principle, some centers create a thigh AVF in preference over an AVG. Sapheno-femoral or transposed femoral vein AVFs have been used in children. These are more likely to have primary failure compared to radial AVF.

Preoperative Planning

Children with CKD, who are expected to be on HD for at least 6 to 12 months, should be referred to a vascular surgeon when the GFR drops below 30 mL/min/1.73 m^2. Early referral is important in children, especially small children, because of long maturation times. The overarching goal should be avoidance of CVC. Dedicated CKD clinics are particularly successful at achieving this goal. Patients who present with ESRD and require an urgent start HD session will need a CVC placed; however, a CVC should be considered as a bridge to permanent access. Patients and parents should be educated about the benefits of an AVF and referred as soon as possible for evaluation of AVF placement if they plan to continue with HD.

Pertinent information in a child with ESRD or advanced CKD being evaluated for vascular access placement includes a history of prolonged hospitalizations and the location and complications of previous central lines. Symptoms of central vein stenosis could include swelling and discomfort of the extremity or face and presence of collateral veins. It is important to note the dominant arm. Physical examination should focus on the presence of scars from previous catheters, extremity edema, collateral veins, and the presence and quality of arterial pulses. The veins are typically examined with more detail, evaluating their length and determining their elasticity. Elasticity of the vein may be assessed with the use of a proximal tourniquet. Morbidly obese patients may present particular challenges in AVF creation with longer surgical and healing time and AVF use due to more difficult cannulation.

Imaging tests are routinely done by some centers; others choose to perform them in select patients. An upper extremity Doppler ultrasound should be done if there are concerns on physical examination. For patients who have a history of previous CVCs and are suspected to have central venous stenosis, it is necessary to perform a venogram. The minimum acceptable vessel diameters for AVF creation are 2.5 mm for veins and 1.5 mm for arteries, although, with the use of microsurgery, successful fistulae have been created with vessels of smaller caliber. When patients are suspected to have central vein stenosis, central vessel imaging with venography or computed tomography venography may be helpful to avoid creating an AVF ipsilateral to a central vein occlusion. Of note, magnetic resonance venography requiring gadolinium administration should be avoided in advanced CKD or ESRD due to the risk of nephrogenic systemic fibrosis.

Surgical Considerations

Young patients need to be sedated or brought under general anesthesia for creation of an AVF. Cooperative adolescents could tolerate the procedure with local or regional anesthesia.

Microsurgery is used routinely for the creation of AVF in children in some European centers and selected cases in other centers. Its use increases success rates, particularly distal AVF in young children (<10 years old) with small arteries. Bourquelot et al., Bagolan et al., Sanabia et al., and Gradman et al., who have reported large European series of children with AVF, achieved functioning radiocephalic AVF with very low failure rates and good long-term patency rates even in small patients (<15 kg). These authors strongly advocate for the use of an intraoperative microscope to create distal AVF in children, as it allows for precise dissection and use of small sutures and avoids the need for dilation of the vessels and causing arterial spasm.

The use of an inflatable tourniquet on the upper arm when constructing a distal AVF is described by some authors to offer additional advantages such as "preventive hemostasis," which results in avoidance of extensive arterial dissection, decreased use of clamps, and lower risk of damage to the intima.

Based on expert opinion, perioperative strategies to optimize early AVF function include starting low-dose daily aspirin at least 1 week prior to surgery, reducing antihypertensive medications in the immediate preoperative period, and directing intraoperative and postoperative fluid management by nephrology to keep blood pressures at or above the 90th percentile for age, height, and gender.

Postoperative Care and Maturation

Hand exercises have been shown to improve maturation in adults and should be encouraged after AVF creation in children old enough to cooperate. Low-dose aspirin is recommended to be continued at least for the first few months after AVF formation. Many pediatric dialysis centers reduce antihypertensive medication doses to allow "permissive" hypertension and carefully maintain adequate intravascular volume by reducing ultrafiltration to encourage maturation.

Maturation times vary widely in pediatric AVF and have been reported anywhere from 4 weeks to 6 months; however, the majority of AVFs in children mature between 8 and 10 weeks. Smaller children tend to have longer maturation times as well as children who have lower blood pressure.

The Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline For Vascular Access: 2019 Update suggests that an AVF is mature in adults when the flow is >600 mL/min, the internal diameter of the draining vein is >6 mm when measured by ultrasound, and the skin-to-vein distance is <6 mm. Pediatric studies have found similar vessel diameter and flow rates indicative of maturation.

Communication between the nephrologist, vascular access surgeon, and HD nurse is imperative at this stage to determine the timing of the first AVF cannulation. Educating the patient and family on proper care of their AVF is of equal importance, especially regarding the need to avoid inadvertent compression of the involved extremity. Multidisciplinary vascular access clinics involving surgeons, nephrologists, dialysis nurses, and ultrasound technicians have shown great success in increasing the number of functioning AVFs long-term.

Cannulation

The first few treatments using a new AVF are usually performed with a 17G needle for cannulation in children. In some instances, single-needle cannulation of the AVF while using one port of the existing CVC can provide a first step strategy to enhance maturation of the AVF to facilitate transition away from the CVC. The pain and anxiety of needling an AVF may also be decreased using this approach in young children. Topical anesthetic creams, applied at home or a few minutes before the scheduled HD session, are useful and may be used routinely. The buttonhole and rope ladder techniques are both used in children; buttonhole cannulation has been associated with a higher incidence of *Staphylococcus aureus* infections in adult studies, so it is being used less frequently in adults. The area technique is no longer recommended as it is associated with higher risk of aneurysmal dilatation, longer bleeding times, and access failure.

Child life specialists may play an important role in cannulation, particularly in the initial cannulation. Although it is possible that children may experience significant pain during cannulation, only about 20% of children report great discomfort, and less than 10% of children report that they would prefer to return to a CVC.

Complications

Primary failure is the most common complication and is reported between 14% and 33% in children, although centers that routinely use microsurgery report much lower failure rates of 5% to 10%. Immediate failure is usually secondary to vessel spasms.

Inflow stenosis (either at the arterial limb, the arteriovenous anastomosis, or at the juxta-anastomotic segment) may lead to low flows and poor quality dialysis and are most commonly resolved with balloon angioplasty. Thrombosis usually occurs secondary to venous stenosis and is the most frequent cause of secondary failure. Postdialytic hypotension can contribute to thrombosis, as well as over compression after needle withdrawal or inadvertent extremity compression between dialysis treatments. Pseudoaneurysms and steal phenomena are less frequent complications, as are AVF infection and high-output cardiac failure. Thigh AVFs may cause significant lower extremity edema in children.

Some AVFs may become quite dilated and appear unattractive, especially radiocephalic AVF, which is easily visible in the forearm.

Long-Term Care and Monitoring of Arteriovenous Fistula

Recommendations for monitoring and surveillance of pediatric AVF are extrapolated from adult evidence as studies are lacking. Monitoring AVF is necessary since stenosis is a common complication and can lead to thrombosis. Children with AVF may be at higher risk due to the smaller caliber of vessels. It is particularly important to preserve functioning vascular access in children to protect potential future access and minimize CVC placement and usage. Monitoring and surveillance of fistulae may detect significant stenosis. A dedicated vascular access clinic allows for early detection of complications and improved patency rates.

Physical examination should be done at each dialysis session; this includes inspection, palpation for a thrill, and auscultating for a bruit. Venous stenosis can be assessed by

elevating the arm; the AVF should collapse if there are no outflow stenoses. The pulse augmentation test evaluates the arterial side and is done by completely occluding the venous limb of the access several centimeters beyond the arterial anastomosis and comparing the pulse between the anastomosis and point of occlusion; an augmented pulse is expected, and if not seen implicates problems with arterial inflow. Problems including swelling of the extremity, hematoma, altered thrill (pulsatile), high pitched bruit, prolonged bleeding after removing needles, difficult cannulation, and aspiration of blood clots should raise suspicion of AVF malfunction and should lead to further evaluation by diagnostic angiography.

Surveillance methods include static and dynamic dialysis venous pressure monitoring, Doppler ultrasound, monitoring intra-access blood flow, and assessing for recirculation. Dynamic venous pressures were not found to predict access thrombosis in a small number of children with AVF. Ultrasound dilution is a noninvasive bedside test to monitor vascular access flow. A sensor is attached to the venous and arterial lines each, and reversing the lines creates recirculation. A saline bolus is then injected via the venous needle into the access flow stream. The sensor on the arterial needle samples the diluted blood and detects changes in ultrasound velocity. Both sensors are connected to a computer, which interprets the changes in Doppler velocity and reports access flow in mL/min. In children, an access blood flow of <650 mL/min/1.73 m^2 has been shown to predict $>50\%$ of access stenosis. Since pediatric HD units are usually small, the cost of specialized equipment for AVF surveillance might be prohibitive, and staff may have to rely on physical examination and venous pressures. A summary of pediatric AVF studies is shown in Table 70.1.

Arteriovenous Graft

Despite AVF being the preferred access for children receiving HD, it may not be the best choice in all situations. AVGs are neither the most common nor the most optimal vascular access choice; as such, their use in adults has not been strongly promoted in the past decade or so. In recent years, though, AVG use has been encouraged in certain situations, including previously failed AVF, poor veins, late referral for vascular access placement with the need for early cannulation, and children in whom AVF is not feasible. The International Pediatric Hemodialysis Network reports that 2% of prevalent HD patients are dialyzed with an AVG. Long-term outcomes of AVG are superior to those of CVCs; however, rates of complications are higher compared to AVFs.

TABLE 70.1 Arteriovenous Fistulae Studies in Children

Reference	Weight (kg)	Use of Operative Microscope	Primary Failure (%)	Primary Patency (%)	Secondary Patency (%)	Complications
Bourquelot 1990	18 (4–48)	Yes	10		85 at 2 years 60 at 4 years	19% of distal AVF had venous stenosis
Sanabia 1993		Yes	10		70% at 5 years for radiocephalic	
Bagolan 1998	28 (6.5–54)	Yes	5	90	70 for >15 kg, 56 for <15 kg at 4 years	Thrombosis 26%, stenosis 4%
Ramage 2005	41.8	No	25		Median survival 3.14 years	
Gradman 2005		Yes		96 at 2 years	100 at 2 years	Thrombosis 6.4%
Briones 2010	27 (10–60)	No	27	50 at 1 year	50 at 2 years	0.84 interventions per 12-access months
Baracco 2014	52 (14.7–113)	No	32.3	42.9	78.1 at 5 years	Thrombosis 20%, stenosis 27%
Wartman 2014	51 (12–131)	Yes		83 at 2 years	92 at 2 years 83 at 4 years	Thrombosis 11%
Onder 2018			13.6			

AVF, Arteriovenous fistula.

Comparison to Arteriovenous Fistula

Although the AVG is considered a permanent internal access, much like an AVF, there are fundamental differences. The AVG is more prone to thrombosis and has higher infection rates than an AVF, particularly lower limb grafts; however, it can typically be used much sooner than an AVF: weeks versus months, respectively. Primary failure rates are higher with AVFs than with AVGs; however, secondary failure rates are higher with AVGs than AVFs. Sheth et al. reported the creation of 24 AVFs and 28 AVGs in 19 and 23 pediatric HD patients, respectively. The primary failure rates were 33.3% and 3.6% in AVF and AVG, respectively. Access stenoses and infection were reportedly higher in AVGs than in AVFs, but thrombotic episodes were not significantly different. In contrast, the morbidity and mortality risk associated with an AVG is similar to that associated with an AVF. Chand et al. evaluated dialysis adequacy (Kt/V, urea reduction rates), anemia management, and albumin status based on vascular access type and found no significant differences between AVFs and AVGs.

Composition

AVGs can be composed of a variety of synthetic materials. Ideally, an AVG should be nonimmunogenic, nonthrombotic, easily placed, quickly accessible, durable, and cost-effective. Over several decades, AVGs have been manufactured from a variety of materials, including saphenous vein, Dacron, cryopreserved femoral vein, umbilical, bovine, polytetrafluoroethylene (PTFE), and polyurethane. While the PTFE AVG is the most commonly used, residual punctures due to cannulation and seroma formation limit its use. Furthermore, due to perioperative graft edema, the PTFE usually cannot be used initially for several weeks. Nagakawa et al. first described the modification PTFE graft by inserting a polyurethane graft segment. This composite graft offers the potential advantage of fewer kinks in the graft conduit, thereby improving efficacy and decreasing stenosis. Additional studies involving this composite AVG in adult HD patients showed no significant difference in operating time, blood loss, or postoperative complications. Less kinking was described with the composite AVG compared to the PTFE AVG. Lau et al. further described the successful use of the composite AVG in a pediatric HD patient without complications from the time of placement to last use 5 months later. As such, some practitioners have chosen alternative AVGs or modified the PTFE graft. Grimaldi et al. reported the successful use of a polycarbonate urethane AVG within 12 hours in a 3-year-old child weighing 12.7 kg. Seven-month follow-up demonstrated continued successful use of the access, with some posterior wall AVG alterations, suggestive of mechanical trauma as a result of repetitive cannulations. Flow and treatment efficacy were not compromised. In recent years, various other modifications have been trialed.

Complications

The primary cause of AVG failure is venous stenosis leading to thrombosis at the graft-vein anastomosis. Ramage et al. conducted a retrospective study over a 20-year period evaluating long-term complication rates of AVFs compared with AVG in children receiving HD. Intervention rates were reported as 17.8% for AVFs and 33% for AVGs. Reasons for discontinuation of AVG use were infection (20%), thrombosis (73%), and planned termination of use (6.7%). Although infection is rare, it can be serious, requiring graft removal. Other potential complications are similar to those seen with AVF and include steal syndrome, aneurysms, and development of neointimal hyperplasia over time.

Central Venous Catheter

Introduction

The advantages of a CVC include immediate access to HD and needle-free dialysis. The disadvantages of a CVC include high infection rate, inadequate flows during dialysis due to malposition and fibrin sheath formation, high rate of replacement due to malfunction or infection, and restrictions on the child's activities (swimming). Catheters have also been associated with high markers of inflammation in children in the absence of infection. Long-term complications include central venous thrombosis and/or stenosis, which can prohibit the successful future placement of an AVF.

Characteristics

The ideal CVC is large enough to allow for adequate blood flow of at least 3–5 mL/kg/min; however, it should not be so large that it obstructs the vein. The catheter tip should end in the right atrium or at the junction of the superior vena cava and right atrium. When the tip of the catheter does not reach down far enough and stays in the SVC, there may be inadequate blood flow as the entry and exit sites of the catheter press up against the vessel wall.

Acute HD access is usually obtained via an uncuffed, nontunneled CVC. The femoral vein is frequently used in patients who are acutely ill and require emergent HD. This site should only be used for a short period of time (<2 weeks; preferably <1 week) as it carries an increased risk of infection, particularly in diapered children.

A cuffed, tunneled catheter is placed for chronic HD—as uncuffed catheters can easily become dislodged in children and are at higher risk of infection. Dual lumen catheters are most commonly used; these are typically made of silicone or polyurethane composites. Split catheters, in which the two catheters are of the same length and separated at the distal end, may be useful in small children in whom the distance between the two ends of a dual lumen catheter are too

far apart to position successfully. The Tesio catheter design consists of two separate catheters of different lengths that are placed in a single vein. The catheters are inserted into a central vein independently.

Location and Placement

The right internal jugular vein is the preferred site for HD CVC. If this site is not an option, alternatives include the right external jugular or left internal jugular veins. Subclavian catheters should be avoided as they have a very high risk of stenosis in children. Even minor stenosis in the subclavian vein can obstruct flow from the ipsilateral extremity and cause future forearm fistula failure. Whenever possible, a CVC should not be placed on the same side as a constructed and maturing AVF.

Occasionally, a child with longstanding CKD and history of multiple CVCs has no central patent veins available for access. In this circumstance, a translumbar CVC could be a better option than a femoral one. The use of lower limb vessels for CVC placement carries the risk of damaging the iliac veins, which could potentially result in technical challenges for the vascular anastomosis of a future kidney transplant.

Placement of HD catheters in children should be ultrasound guided and performed by either surgeons or interventional radiologists. Ultrasound guidance reduces the risk of immediate complications, especially in patients with anatomic variations of the internal jugular vein. Fluoroscopy is typically used to confirm the position of the catheter tip once the procedure is completed.

Infants and Small Children

Two-catheter HD may sometimes be required in infants, particularly in an emergency situation. The catheters are placed in the femoral veins; the tip of one is positioned in the inferior vena cava and the other in the internal iliac vein to decrease recirculation. This strategy is only useful, however, for a few dialysis sessions. Another option in infants is to use a single lumen catheter and split it into afferent and efferent lines using a Y connector. This allows for higher blood flows when compared to a double lumen catheter of the same size. The blood flow is controlled by two pumps—or a single pump and a valve, to alternate drawing and returning blood. There will be some recirculation with this system, which is proportional to the length of the line between the Y connector and the patient.

Successful continuous renal replacement therapy has been performed in ill neonates and infants with cardiac disease using a two venous sheath technique. The sheaths, most of which were 4 Fr and placed in both femoral veins, provided high blood flows and allowed for uninterrupted dialysis. Catheter options for pediatric patients are listed in Table 70.2.

TABLE 70.2 Central Venous Catheter Sizes for Children on Hemodialysis

Patient Weight	CVC
Newborn	7 Fr dual lumen
5–20 kg	8 Fr dual lumen
20–40 kg	7 Fr Tesio (20–25 kg)
	10 Fr dual lumen
	10 Fr split catheter
	10 Fr Tesio catheter
	11.5 Fr dual lumen (>30 kg)
>40 kg	10 Fr Tesio
	11.5 Fr dual lumen
	12.5 Fr dual lumen

CVC, Central venous catheter.
Adapted from KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for 2006 Updates: Hemodialysis adequacy, Peritoneal Dialysis adequacy and vascular access. *Am J Kidney Dis*. 2006;48:S1–S322.

Long-Term Care

The CVC exit site should not get wet. This limits the ability of the child to be able to swim. Cleaning of the exit site should be performed at least once weekly. A pediatric study found that cleaning the exit site once weekly versus three times a week was associated with fewer infections; however, this needs to be confirmed with prospective studies. Most centers use a chlorhexidine gluconate (CHG)/alcohol-based solution, which has been shown to be superior to iodine solutions in prevention of infection. Topical antimicrobial ointments such as mupirocin, polysporin, and povidone-iodine are used on the skin near the exit site to reduce infection.

The CVC lock varies between centers, with the majority of pediatric dialysis units using heparin in concentrations from 1000 U/mL to 5000 U/mL. Some pediatric units use tissue plasminogen activator (t-PA). The use of t-PA instead of heparin at the midweek session of HD in adults has shown to decrease the risk of catheter malfunction and bacteremia. The European Society for Pediatric Nephrology consensus for vascular access in children on chronic HD suggests t-PA as a locking solution to prevent CVC thrombosis. However, the higher cost of t-PA compared to heparin may be a limiting factor to this practice.

There have been several cases of children who had hemorrhagic complications from inadvertent anticoagulation with the use of 5000 U/mL heparin lock flush. Despite efforts to administer heparin exclusively within the catheter lumen based on the predetermined "lock volume," CVCs can have a substantial amount of leak/overflow (~15%) into the systemic circulation. Because of their small size, children need only a very small amount of high-concentration

TABLE 70.3 Care of Hemodialysis Central Venous Catheter

1. Catheters should be accessed only by experienced dialysis personnel
2. Clean exit site with chlorhexidine gluconate (CHG)/alcohol-based solution
3. When using heparin to lock CVC, 1000 U/mL concentration is preferred
4. Measure aPTT prior to any procedure
5. Avoid flushing catheter in the perioperative period
6. Avoid using catheter for intravenous fluids/medications or blood draws

aPTT, Activated partial thromboplastin time; *CVC*, central venous catheter.

heparin to become systemically anticoagulated, so they are at particularly increased risk.

Between dialysis treatments, it is preferable to not use the CVC for intravenous access (fluids, medication administration, or blood draws) unless in the event of an emergency, as the risk of infection increases with each time the catheter is accessed. HD catheters should only be accessed by nurses who are trained and experienced in HD. Table 70.3 summarizes recommendations for the care of CVC in children.

Complications

Acute complications when placing a CVC include inadvertent arterial puncture, air embolism, pneumothorax, hemothorax, and bleeding. The most common long-term complications, often leading to removal of CVC, are malfunction, thrombosis, and catheter-related bacteremia. Infection rates have been reported from 1.5 to 8.6 bacterial infection episodes per 1000 catheter days. Thrombosis is initially treated with t-PA, which is an effective thrombolytic agent. Longer t-PA dwell times are associated with greater efficacy. Other long-term complications include central venous stenosis and fibrin sheath formation. Accidental extraction is another complication that can occur in children.

Antibiotic lock solutions have been reported to decrease exposure to systemic antibiotics when used prophylactically in children at increased risk for CVC-related bacteremia. Tobramycin mixed with anticoagulant at a concentration of 5 mg/mL has been used to lock HD catheters one to three times a week.

Peritoneal Dialysis Access in Children

According to the 2018 annual data report from the U.S. Renal Data System (USRDS), the prevalence of ESRD children (0–21 years of age) in the United States was 9721 as of December 31, 2016. In contrast to adults, peritoneal dialysis (PD) is used more frequently in children and is the most common initial renal replacement modality in children 9 years of age and younger. PD has distinct advantages over HD due to its universal applicability, lower cost, and ease of procedure. The ability to perform the treatments at home causes less disruption to the family's lifestyle.

PD catheters can be used short- and long-term. The optimal catheter allows for maximum dialysate flow, with minimization of catheter movement with no consequent leaks. The ultimate goal is to maintain PD without infections (exit site, tunnel, or peritonitis) with adequate solute and fluid removal to allow optimal child growth.

Peritoneal Dialysis Candidate

While a functional peritoneal membrane is a requirement, absolute contraindications to PD include structural abnormalities including omphalocele, gastroschisis, bladder exstrophy, diaphragmatic hernia, or other peritoneal cavity abnormality. Relative contraindications include impending or recent major abdominal surgery and social impediments, including lack of a reliable caregiver. The presence of a gastrostomy tube, augmented bladder, and ureterostomy are no longer viewed as contraindications; however, if present, they must be considered in the placement and use of the PD catheter.

Surgical Consultation

The need for renal replacement therapy may be anticipated in the setting of progressive CKD, or in other instances, the presentation may be acute and not allow the luxury of advanced planning. The surgeon should be consulted as soon as the need for dialysis is recognized.

In the setting of an urgent start dialysis, the PD catheter can be placed and used immediately. In this circumstance, low dialysate fill volumes should be used initially so as not to compromise the surgical healing and precipitate leaks. Dialysis can be performed continuously with these low fill volumes, which are increased incrementally at slow rates every 2–3 days as tolerated.

However, in a nonurgent situation, the preference would be to delay starting PD for 2–3 weeks post catheter placement to allow for proper anchoring of the cuff(s) and healing of the exit site. Low intra-abdominal pressure allows adequate wound healing, especially in infants who have minimal subcutaneous tissue.

The surgical consultation should include evaluation of anesthetic risk and review of prior abdominal surgeries to gauge feasibility. Imaging can be considered if the patient has had multiple prior surgeries to understand better the surgical approach that should be taken. Adhesions can be evaluated using ultrasound to determine the extent of internal scarring. This can allow for the selection of optimal surgical approach and location. For example, if a patient has had a prior appendectomy, placing the PD catheter on the left side would be preferred.

Patient Preparation

Patient conditions that should be ameliorated include the resolution of constipation and repair of hernias. As constipation can predispose to catheter migration and/or malfunction, a proper bowel regimen should be implemented in anticipation of surgery. This may include treatment of chronic constipation while also administering an intensive bowel preparation immediately prior to catheter placement to allow for optimal postoperative function. It is imperative to avoid phosphate-containing enemas in children with ESRD.

Inguinal hernias due to patent processus vaginalis are common in male infants and even more so in premature infants. If possible, these hernias should be repaired prior to or at the time of catheter placement to mitigate the risk of worsening the hernia after PD initiation. The processus vaginalis may be ligated if the testes are descended. Umbilical hernias may occur and, if present, can be repaired at the time of catheter placement.

Catheter Types

While the International Society for Peritoneal Dialysis (ISPD) 2019 Guidelines/Recommendations apply to adults, there are several principles that are applicable to children. The key variables in catheter design include material (silicone vs. polyurethane), catheter tip (straight vs. curled), number of Dacron cuffs (single vs. double), and exit site position (upward vs. downward vs. lateral). The ISPD recommends silicone catheters with two Dacron (polyester) cuffs but does not give firm recommendations regarding straight versus coiled tip, nor are there recommendations made in favor of a straight versus swan neck subcutaneously tunneled configuration.

Perioperative and Intraoperative Considerations

When preparing a patient for placement of a PD catheter, proper perioperative planning should entail:

1) finalization of ideal catheter type and location (including mapping of the catheter route);
2) aggressive preoperative bowel regimen to reduce risk of constipation;
3) bathe with a minimum 2% chlorhexidine soap on day of scheduled surgery;
4) bladder decompression prior to surgery from spontaneous voiding or urinary catheter; and
5) single intravenous dose of vancomycin to reduce risk of postoperative peritonitis.

PD catheter placement in the pediatric patient is performed using general anesthesia. Operative placement of a PD catheter in children is either done by an open surgical approach versus laparoscopic placement.

Intraoperative recommendations to optimize catheter placement include skin preparation with chlorhexidine gluconate or povidone iodine to prevent a surgical site infection. The catheter tip should be placed in a pelvic location. A purse-string suture incorporating the deep cuff is placed at the level of the posterior sheath of the rectus muscle, anchoring the catheter. The catheter exit site should be greater than 2 cm beyond the superficial cuff, which should be placed in the anterior sheath of the rectus muscle. There should be no catheter anchoring sutures at the exit site. The goal is to have the rectus muscle anchor the catheter cuffs.

A partial omentectomy should be performed with all PD catheter placements due to the high risk of catheter occlusion. Because the omentum is attached to the transverse colon, performing an omentectomy below the level of the umbilicus decreases the likelihood of catheter occlusion.

The ideal surgical placement is to place the catheter tip in the pelvis. Of note, a catheter tip placed deep into the pelvis adjacent to the pelvic structures (bladder and rectum in males or uterus and rectum in females) can result in pain at the end of the drain cycle. In children, a downward or lateral exit-site position is acceptable; further, the exit site should be located outside of the diaper region. If applicable, precautions should be taken to keep the PD catheter exit site distant from neighboring -ostomy sites (e.g., gastrostomy, colostomy, etc.). The exit site should be covered with a nonocclusive dressing.

The PD catheter should be assessed immediately after placement in the operating room. The catheter should be flushed until the dialysate runs clear and the catheter filled with heparinized saline or heparinized dialysate to mitigate fibrin occlusion of the catheter. The peritoneal cavity should be filled, and then the catheter allowed to drain to gravity to assess for proper flow. The catheter should not be left empty but rather filled with the heparinized solution. An adapter and transfer set should be placed under sterile technique by the surgical team prior to leaving the operating room.

Postoperative Management

In circumstances of delayed initiation of dialysis, flushing the catheter periodically to assess patency is a practice conducted at some dialysis centers; conversely, other centers elect to leave the catheter untouched until the time of use for dialysis. The decision to flush or not flush a resting catheter is individualized by the center in the absence of randomized controlled trials. Postoperative dressing changes should be performed regularly by trained personnel.

The most common early complication in children is mechanical malfunction, which presents as either failure to drain or catheter leak. Potential causes of drain failure include omental obstruction, catheter migration out of the pelvis, or catheter occlusion by fibrin. Catheter kinking may occur and, if suspected, can be evaluated using imaging (flat-plate and lateral abdominal x-rays). Constipation and bladder distention should be excluded as medically treatable causes of obstruction and failure to drain. Any true mechanical malfunction will likely require a return to the operating room to rectify, often done laparoscopically. With early

intervention, catheter function can usually be preserved without consequence.

Pericatheter fluid leaks can occur within hours to weeks of placement and are usually due to improper implantation, premature use of the catheter, or trauma. Ultrasound can be used to evaluate the leak. Temporary cessation of dialysis often suffices to resolve the leak, and therefore, dialysis should be held as long as feasible to ensure proper healing. When resuming dialysis, low fill volumes are strongly recommended with slow advancement based on dialysis needs.

Infections are a potentially serious complication that jeopardizes catheter life and long-term peritoneal membrane viability. Early detection and treatment of exit-site tunnel infection may prevent extension into the peritoneal cavity. Peritonitis should be treated promptly to avoid membrane scarring. The management of infectious complications is discussed elsewhere in this handbook.

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71

Infant Hemodialysis

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Vascular Access

Hemodialysis requires a central venous catheter, and in infants, this poses technical challenges because of their smaller vessel size and the likelihood that they may require vascular access throughout their lifetime if end-stage renal disease is present. Dialysis catheters are stiff, allow for high rates of blood flow, and are relatively larger than other central lines. Thus, use of central lines other than those designed for dialysis is not recommended. Historically, umbilical lines were sometimes used for infant hemodialysis access, but this has fallen out of favor with the availability of small-diameter hemodialysis lines. If umbilical vessels are used, the umbilical artery must have at least a 5-Fr (French) catheter and the umbilical vein, at least a 7–8-Fr catheter. In this case, the tip of the umbilical vein catheter should be above the diaphragm, and the tip of the umbilical artery catheter should be below the renal arteries. If umbilical catheters are used for dialysis, the arterial and venous lines cannot be reversed.

The choice of a temporary (uncuffed, nontunneled) versus semipermanent (cuffed, tunneled) hemodialysis catheter depends on whether the infant is expected to require short- or long-term therapy. However, even if the infant is expected to require long-term dialysis, many will be transitioned to PD, and thus in the acute setting, a temporary catheter (uncuffed) is often placed. Placement of a hemodialysis catheter should be performed under fluoroscopy to confirm placement. The line with the largest possible gauge should be placed in order to allow for optimum blood flows. However, placement of a line that is too broad can result in occlusion of the vessel. Available catheters may differ across institutions. Typically, the smallest catheter that can be used for hemodialysis and still maintain adequate blood flow is 7–8 Fr.

Options for the location of the HD catheter in infants include internal jugular (IJ), subclavian, and femoral veins. Catheter insertion sites should be determined individually as each infant requiring hemodialysis may have specific circumstances precluding one site or another. Use of the subclavian vein should be avoided if a line can be placed in the IJ, as occlusion of the subclavian vein may preclude creation of an arteriovenous fistula when the child is older and may require additional dialysis access. Ideally, the tip of the catheter should be at the right atrium/superior vena cava junction when placed in the IJ or subclavian. Catheters in the femoral vein should have the tip as central as possible. Femoral catheters are associated with an increased risk of infection and thus should not be used long-term. With noncentral placement of catheters, there is an increased risk of recirculation as well as blood flow limitations.

Complications of hemodialysis access include infection, clotting, venous outflow obstruction, and failure of the access, which may be related to mal-positioning or movement, kinking, or breaking of the line. Because these complications result in an inability to provide dialysis and may require surgical replacement of the line, only trained dialysis staff should use dialysis lines. Anticoagulation is used during dialysis to maintain patency of the lines, and the details of this are reviewed in Chapter 74. Additional information regarding access may be found in Chapter 72.

Equipment/Preparation

Equipment for hemodialysis includes dialysis machines, blood lines, and dialyzers. Each must be carefully considered to provide the safest and most efficient treatment for the infant. Many dialysis machines will now allow low blood flows, although none provides specific indications for infant dialysis, and thus provision of infant dialysis is an off-label use of the machine. Use of newer machines created for infants is typically geared toward continuous renal replacement therapy (CRRT), which is discussed elsewhere. Of critical importance in selecting a dialysis machine to use for the infant is the availability of accurate control of ultrafiltration. In the infant, even small volumes of ultrafiltration may result in hemodynamic changes. The ordering clinician should know the margin of error for ultrafiltration for each type of machine used.

One must have accurate information regarding the priming volume of the blood lines and the dialyzer. This should be available on standard packaging. The priming volume of the dialyzer and blood lines should never exceed 10% of patient's blood volume. For small patients, use of blood to prime the circuit may be required to avoid hemodynamic

compromise and hemodilution. Use of neonatal lines may allow the clinician to reduce or avoid blood primes. If a blood prime is required, an aliquot of packed red blood cells should be diluted to achieve a priming hematocrit of 35%–45%. Consideration when using blood primes includes the potential for sensitization when exposing an infant to multiple blood donors, which may complicate future transplantation. Donated blood is anticoagulated with citrate, which may lead to hypocalcemia in the infant, and thus, serum calcium should be assessed and supplemental calcium provided if indicated. Blood primes also contain a significant amount of potassium, and, if possible, one should use fresh blood or washed red cells to avoid hyperkalemia. At the end of a treatment initiated with a blood prime, blood in the lines is not returned to the patient as this would represent a large-volume transfusion and can lead to hypervolemia, hypertension, and/or pulmonary edema. If the prime volume is less than 10% of the blood volume, 5% albumin may be used for priming. Lines may need to be warmed to prevent hypothermia in the infant undergoing hemodialysis. Frequent temperature monitoring is required.

For infants undergoing hemodialysis, typically, the smallest dialysis filter available is appropriate, as smaller filters will still allow for adequate clearance given the low total blood volume. There are a wide variety of filters with various blood volumes available, and each institution may have its own preferable filters based on local experience. Given the low number of small children receiving hemodialysis each year, there are no formal studies comparing the safety and efficacy of different dialysis machines and filters in infants.

Dialysis Prescription for the Infant: Special Considerations

Infants undergoing hemodialysis require special considerations when developing the dialysis prescription with regard to the clearance, blood flow, and other parameters (Table 71.1).

TABLE 71.1 Requirements for Infant Hemodialysis Prescription

- Dialyzer/filter size
- Blood flow (Q_b)
- Dialysate flow (Q_d)
- Sodium program/modeling
- Prime solution (blood/albumin vs. albumin vs. saline)
- Anticoagulation (heparin, citrate, other, none)
- Length of treatment (min)
- Ultrafiltration goal (mL and mL/h)
- Blood products and medications to be administered during treatment

Rapidly lowering the blood urea nitrogen (BUN) with hemodialysis may result in disequilibrium syndrome. Complications can also arise in infants who are hyperosmolar due to hypernatremia. Thus, a stepwise approach should be used in those with marked uremia or hypernatremia by providing increasing clearance each day to allow for gradual equilibrium. Initial clearance for an infant with significant uremia should be limited to provide no more than 30% urea reduction rate on the first day, followed by sequential increases in urea reduction (30%, 50%, 70%) to avoid disequilibrium. If the desired ultrafiltration cannot be achieved in the same time frame, one can continue with ultrafiltration only to achieve the desired effect or consider other modalities of dialysis, such as one of the modes of CRRT. Dialysis initiated for removal of other substances, for example, ammonia without significant uremia, should focus on removal of that particular substance. In this case, maximal clearance should be attempted with each therapy, including the initial treatment. If the infant's BUN is very high, but clearance for removal of other solutes is required, one can infuse mannitol through the dialysis circuit to avoid rapid osmotic changes and thus prevent disequilibrium and cerebral edema.

Blood flow for hemodialysis in the infant should be 6–8 mL/kg/min. However, in the smallest infants, this may still be insufficient to maintain blood flow through the circuit. The lowest blood flow for most machines is 25 mL/min, and thus the blood flow range should be limited to 25–50 mL/min. Higher flow rates in the infant can lead to cardiovascular collapse. Lower blood flows will increase the risk of clotting, and thus if the infant can tolerate blood flows of 50 mL/min, this is preferred. At low blood flow rates, the dialyzer clearance of the solute for the blood flow through the circuit will be equal to the blood flow rates for calculating the time needed to achieve a particular clearance. After each treatment, using the urea reduction rate achieved, one can back-calculate the actual clearance of urea and use this for calculating the next prescription based on a recalculated volume of distribution.

Dialysate flow should be at least two times the blood flow to provide optimal countercurrent gradient for clearance of molecules. In many institutions, the dialysate flow is set at a minimum of 300 or 500 mL/min. Hemodialysis can result in lowering the infant's core body temperature. Thus blood lines and dialysate may be warmed to avoid hypothermia. Conversely, in cases of malignant hyperthermia, room temperature or cooled blood lines may be used to lower core temperature.

Anticoagulation

Anticoagulation for dialysis is discussed in detail in Chapter 74. However, there are specific considerations for the infant undergoing hemodialysis, which will be discussed here. Heparin is often used to anticoagulate the system and minimize the risk of clotting. Use of heparin poses risks in

the neonate, including intracranial hemorrhage and bleeding from surgical sites. Infants with preexisting conditions such as bleeding or recent surgery may require hemodialysis sessions without heparin. In this case, frequent flushes of saline can be provided prefilter to prevent clotting, and the volume of the flushes can be removed by ultrafiltration. Use of citrate for anticoagulation poses the potential risk of hypocalcemia and requires close monitoring with calcium supplementation.

Frequency

Although most patients receiving chronic hemodialysis typically undergo three sessions each week, the infant undergoing hemodialysis will require more frequent treatments. Infants in the intensive care unit should undergo daily dialysis to allow for a more stable metabolic balance and provision of ultrafiltration to ensure they can receive adequate nutrition without worsening fluid overload.

Ultrafiltration and Clearance

Ultrafiltration should be limited to no more than 5% of the infant's dry weight in each dialysis session. If more ultrafiltration is required in the acute setting, one can consider the use of CRRT to provide slow continuous removal of fluid rather than attempting to remove a large volume of fluid in the time on intermittent dialysis. If ultrafiltration is required despite the need to avoid excessive clearance, such as in the case of significant uremia, dialysate can be stopped once the desired clearance is achieved, and one can continue ultrafiltration alone, as noted previously. In this case, there will be a small amount of clearance due to solvent drag/convective clearance.

When dialyzing infants, the rate of ultrafiltration volume must be considered relative to the size of the infant and effective circulating volume. In most institutions, ultrafiltration should not exceed 100 mL/h. Thus treatment time may be extended beyond that required for clearance to allow for adequate ultrafiltration. Before and after a treatment, the infant's weight should be measured on an infant scale. Bed scales will not be sensitive enough to detect small changes that are clinically significant in the infant. Furthermore, current dialysis machines may not report precise ultrafiltration volumes, and small margins of error could be significant to the infant undergoing hemodialysis. If the infant becomes hypotensive and volume is required to reestablish effective circulating volume, fluids can be administered in increments of 10–20-mL boluses, in the form of normal saline, 5% albumin, or blood, depending on the situation.

High rates of clearance can lead to hypokalemia, hypophosphatemia, and other electrolyte derangements. Close monitoring of electrolytes and repletion as needed, as well as adjustment of dialysate to avoid life-threatening electrolyte abnormalities, is paramount to the care of the infant receiving hemodialysis. Many vasopressors and sedatives will be cleared with hemodialysis. Thus the primary team should be prepared to increase the doses of these medications as needed while the infant is receiving hemodialysis. Antibiotics and other medications may need to be dose-adjusted when the infant is receiving hemodialysis. Consultation with a pharmacist familiar with such treatments may be useful. Otherwise, drug-dosing resources can be used to determine whether dosing adjustments are required. Medications for which levels are monitored should be assessed after the patient has reached equilibrium, typically 4–6 hours after completion of the HD session, or sooner if the clearance with dialysis is predictable.

Blood products and medications often result in large volumes being administered to the infant. Furthermore, these may provide additional potassium and sodium load. Thus transfusion of blood products to the infant with renal failure should be done while on dialysis when possible. If other medications require a large volume but are not dialyzed, they can be provided during dialysis and the volume removed by ultrafiltration to result in no net fluid administration to the patient.

When considering dialysis for toxin ingestion or overdose, it is critical to review the toxin and its metabolites to determine what will be cleared. Substances that are dialyzed most easily are those that are water-soluble, low molecular weight, and not protein bound. However, some toxins that are protein bound may have metabolites that are present in a free state, and thus assessment of the utility of dialysis should be undertaken on a case-by-case basis depending on the compound in question. Dialysis performed for indications other than renal failure, such as hyperammonemia, often requires a different approach and may require maximizing clearance beyond that which is recommended for infants with renal failure. In this case, one does not need to consider disequilibrium as the patient is not typically uremic, and removal of the solute or toxin may dictate changes to the dialysis prescription. Dialysis for infants with inborn errors of metabolism is discussed in Chapter 78.

Modality

Patients who require hemodialysis in the acute setting may be transitioned to peritoneal dialysis (PD) if they will be dependent on renal replacement therapy in the long term. In such cases, a PD catheter can be placed at the time of HD catheter placement if such information is known or later. If a PD catheter will be required, it is preferable to place this as early as possible to allow for adequate healing prior to use. HD can continue until the PD catheter is healed and ready for daily use.

Intermittent hemodialysis can be provided via the ECMO circuit in the infant requiring ECMO. In this case, higher blood flows can usually be achieved as the flow through the ECMO circuit is on the order of 100 mL/kg/min. When performing dialysis via the ECMO circuit, one must take into account the volume of distribution, which includes the

ECMO circuit. Ultrafiltration is usually not performed via the HD circuit in this case, as it can be achieved via the ECMO circuit continuously.

Chronic Hemodialysis

The infant requiring chronic hemodialysis is at increased risk of mortality. In this case, meticulous attention to growth and nutrition is required and is best accomplished with the use of a multidisciplinary team to assess all needs of the infant. This team should include a pediatric nephrologist, experienced pediatric dialysis nurses, a renal dietitian, a social worker, and a pharmacist if possible. Infants undergoing hemodialysis who are otherwise not critically ill will still typically require at least four to five sessions per week to allow for adequate nutrition and growth. Urea kinetic modeling is used to determine dialysis adequacy and is described in detail in Chapter 72.

Recommended Reading

Goldstein S. Advances in pediatric renal replacement therapy for acute kidney injury. *Semin Dial.* 2011;24(2):187–191.

This review addresses the requirements specific to children and infants requiring renal replacement therapy.

Raina R, Vijayaraghavan P, Kapur G, et al. Hemodialysis in neonates and infants: A systematic review. *Semin Dial.* 2018 May;31(3):289–299.

This review summarizes several studies reporting on infant hemodialysis with data regarding clinical characteristics, outcomes, technical considerations, maintenance, and complications associated with provision of HD in the infant.

Rees L. Renal replacement therapies in neonates: issues and ethics. *Semin Fetal Neonatal Med.* 2017;22:104–108.

This review summaries the issues arising in providing dialysis to neonates, including technical issues as well as ethical challenges.

Sebestyen J, Warady B. Advances in pediatric renal replacement therapy. *Adv Chronic Kidney Dis.* 2011;18(5):376–383.

In this review, a detailed discussion of vascular access and technical aspects of peritoneal and hemodialysis in children is provided.

Vidal E, Stralen K, Chesnaye N, et al. Infants requiring maintenance dialysis: outcomes of hemodialysis and peritoneal dialysis. *Am J Kidney Dis.* 2017;69(5):617–625.

This report summarizes data from the ESPN/ERA-EDTA registry of infants 12 months and younger who initiated dialysis over a 22-year period.

Warady B, Neu A, Schaefer F. Optimal care of the infant, child, and adolescent on dialysis: 2014 update. *Am J Kidney Dis.* 2014;64(1):128–142.

A narrative review encompassing all aspects of care for the child with end-stage renal disease. This includes recommendations regarding vascular access and treatment of infections, as well as evidence that children who undergo more frequent dialysis than thrice weekly demonstrate improved control of anemia, mineral, and bone disorders, hypertension, and fluid status as well as improved growth and nutrition.

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Urea Kinetic Modeling for Hemodialysis Prescription in Children

AVRAM Z. TRAUM, MD • MICHAEL J.G. SOMERS, MD

Chronic Hemodialysis in Children

Although renal transplantation is the optimal treatment for end-stage kidney disease in children and adolescents, many pediatric patients nonetheless must spend some time on chronic dialysis. Historically, a much larger proportion of children than adults undergo peritoneal dialysis, but registry data from the U.S. Renal Data System (USRDS) and the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) suggest that the proportion of children with end-stage renal disease (ESRD) receiving hemodialysis (HD) has increased. In NAPRTCS cohorts from 1992–2001 and 2002–11, 35% and then 42% of children, respectively, used HD as an initial dialysis modality.[1] With more recent USRDS data from 2019, among incident dialysis patients from infancy up to age 21 years, 65% were receiving HD, and the choice of HD as a preferred modality was similar in prevalent patients of an equivalent age range at 62%.[2] As a result, clinicians caring for children and adolescents on dialysis must be familiar with assessing HD adequacy and cognizant of the value of urea kinetic modeling in formulating HD prescriptions. Moreover, quality measures stipulating HD adequacy standards for children are now endorsed by many health care improvement organizations, and pediatric dialysis adequacy measures have been included in the ESRD Quality Incentive Program administered by the Centers for Medicare & Medicaid Services (CMS) in the United States.

Despite this increased focus on dialysis adequacy in children, limited data on long-term outcomes of dialyzed children continue to exist, especially analyzed in the context of certain standards of adequacy. The 2006 National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines for HD adequacy acknowledged this issue.[3] They specify that because of limited specific pediatric data, many recommendations are based on extrapolation from the much broader experience in adults. In the 2015 update of these guidelines, dialysis adequacy in children was not even mentioned. Unfortunately, many outcome measures looking at dialysis adequacy in adults are focused on narrowly assessing mortality rates or specific organ system morbidity over time and do not consider clinical variables of special import to assessing the adequacy and effectiveness of renal replacement therapy in children, such as somatic growth and development, cognitive and emotional maturation, and school attendance and performance.

As dialysis adequacy guidelines are applied more broadly to children with ESRD for both clinical care and assessment of quality care, it is incumbent on pediatric clinicians to determine whether adult standards really do define a proper dose of dialysis for children and to then assess further the applicability of these current standards to appropriate long-term outcome measures. Along these same lines, as new methods of assessing dialysis adequacy are proposed and considered, their application and usefulness to children on HD should be analyzed with pediatric-specific data as well.

Dialysis Prescription in Children

Because clinicians caring for children with ESRD will be prescribing dialysis to patients whose size and weights may vary 20- or 30-fold, there is much more of an individualized focus on the dialysis prescription in children than in adults. For instance, the HD prescription for an 85-kg adolescent will differ dramatically from the treatment given to a 5-kg baby, which will, in turn, be quite different from the prescription for a 25-kg elementary school student. Because children receiving dialysis are more likely than adults to have broad variations in size and total blood volume (which in turn affect many technical aspects of safe and successful HD provision), the quantity of dialysis that a child receives needs to be more precisely calculated and readjusted. Moreover, as the child grows, the prescription must be reformulated, mindful of ongoing changes in total body water and evolving nutritional requirements.

Similar to adults receiving chronic HD, urea kinetic modeling is used in children, both to serve as an objective measure of HD adequacy and to monitor nutritional adequacy by allowing for the determination of protein catabolic rate (PCR). With this approach, urea clearance is used as a

surrogate to reflect removal of low-molecular-weight uremic toxins, and the interdialytic rise in urea levels can be used to estimate protein catabolism. The choice of urea as a marker stems from its relatively even distribution over the total body water, its low molecular mass and ensuing ready dialysis clearance, and its status as the principal constituent of nitrogen waste that accumulates in body water. The extent of clearance of urea from body water has been correlated with morbidity and mortality outcomes.

One of the prime advantages of urea kinetic modeling is that it provides quantitative data that is not only reproducible but can also guide the individualization of dialysis prescriptions. Most notably, urea kinetic modeling elucidates disparities between expected or calculated doses of dialysis and actually delivered dialysis. A major disadvantage of kinetic modeling is the need to coordinate obtaining specific data at stipulated time points. Depending on local resources, these maneuvers may be relatively labor and time intensive and may add cost to the chronic therapy. Although the calculations for kinetic modeling are complicated, numerous web-based programs or electronic applications exist that simplify the compilation of necessary data and facilitate computation of overall adequacy rapidly.

There has also been controversy as to whether the adequacy of dialysis is best measured using a single- or double-pool model of estimated volume. In a single-pool model, the clearance of urea from the blood volume may overestimate the dose of dialysis measured by kinetic modeling because blood measurements are performed before effective re-equilibration of urea from the intracellular space into the intravascular space (urea rebound). This concern is especially true in children with smaller distributions of urea which are dialyzed with filters with the capability of high rates of solute clearance.

On the other hand, the need for patients to remain for a substantial period after the dialysis treatment is completed to draw a re-equilibrated postdialysis blood urea nitrogen (BUN) adds another layer of logistical complexity to utilization of a double-pool model. There are some data suggesting that for the majority of children generally able to achieve relatively high levels of Kt/V, the discordance rate between single-pool and equilibrated values does not impact the ultimate management of adequate dialysis prescriptions.[4]

While the Kt/V of urea is generally used to assess dialysis adequacy, Daugirdas has reviewed a variety of other approaches.[5] He describes a number of drawbacks of spKt/V, including its limitations in patients receiving HD at frequencies other than three times a week and challenges in harmonizing weekly Kt/V values derived in peritoneal dialysis patients with those receiving HD. This intriguing review compares other models based on such parameters as body surface area versus volume of distribution, total weekly time spent on HD, and the role of nonurea solutes such as phosphorus, middle molecules, and other uremic toxins. The use of what is termed a "standard Kt/V" has been endorsed by some guidelines in those situations where dialysis is occurring at some frequency other than three times a week.

It remains incumbent on the clinician prescribing chronic dialysis to be aware that a patient's particular dialysis regimen and any residual renal function need to be kept in mind when assessing dialysis adequacy and setting targets for adequacy. For instance, children receiving dialysis four or more times a week or children with substantial native residual renal function will need to have these extra sessions and their native kidney function included in both the calculation of dialysis adequacy and setting of dialysis adequacy targets for an individual dialysis session. As noted earlier, although this necessitates the use of more complex calculations than with typical estimation of dialysis adequacy, the ready availability of dialysis adequacy programs and applications that take into account these variables allow for these individualized approaches.

Principles of Urea Kinetic Modeling in Children

The theoretical principles of urea kinetic modeling are identical in children and adults. The rate of removal of any solute from the intravascular space using HD can be modeled by considering the intrinsic permeability properties of the dialyzer, circuit specifics such as blood and dialysate flow, and physical and biochemical properties of the solute to be removed. The dialyzer's most important characteristic is its permeability surface area product (generally abbreviated as K_0A), which is dependent on the blood flow (K_D) delivered through the dialyzer defines its potential clearance of the solute in question. This variable defines the dialyzer's ability to remove the solute in question.

The following mass transfer equation can be set up and solved to quantify the physical removal of any solute in question during dialysis:

$$C_T = C_0\left(e^{-Kt/V}\right) + G/K\left(1 - e^{-Kt/V}\right)$$

Here, C_T is the solute concentration at any given time during the dialysis treatment, C_0 is the concentration of the same solute at time 0 or dialysis initiation, K is the dialyzer clearance of the solute for the blood flow through the circuit, t is the duration of dialysis in minutes, V is the volume of distribution of the solute, and G is the ongoing generation rate of the solute. Although this equation can be applied to any solute of interest, its application to urea removal is the underpinning of urea kinetic modeling, and the calculated Kt/V has been used as the measure of the dose of dialysis delivered or the fractional clearance of urea for the patient's volume of distribution.

There are a number of applications of this equation toward changes in metabolic balance. If all variables are known, BUN concentration can be calculated for any time point during the dialysis session. Similarly, with the necessary variables known, V and G can be calculated using BUN measurements acquired at varying time points during the dialysis treatment.

When G is known, the PCR can be calculated using the equation

$$PCR = 6.5G + 0.17(Wt)$$

where PCR is expressed as grams of protein per day, G is grams of urea per day, and Wt is the patient's weight in kilograms. The PCR can be used along with clinical variables such as growth and laboratory parameters such as serum albumin to help assess nutritional adequacy. A PCR near 1 is considered ideal for most children. Although adequate dialysis helps improve appetite and nutritional intake in patients receiving chronic HD, there is no evidence that higher doses of dialysis improve nutritional status.

Data Collection

Generally, data are collected over a number of HD sessions to calculate V and G. The remaining variables in the equations are known or can be easily determined. For instance, BUN is measured at the start of an HD session (C_0), at the end (C_T or C_1), and again at the start of the next session (C_2). This pattern helps to define the intradialytic and interdialytic fluxes in BUN, which provide information as to urea reduction rate (URR) during dialysis, residual renal function with accompanying clearance of the solute in question during and between dialysis sessions, and ongoing generation of urea from protein catabolism. The following variables make it possible to predict BUN at any point in time.

- *K_D, dialyzer clearance:* This is a function of the dialyzer (K_0A), blood flow (Q_B), and dialysate flow (Q_D). The measured rather than the prescribed blood flow should be used for calculations.
- *K_R, residual renal function:* This variable is generally measured initially and then at regular intervals unless a change occurs that would suddenly impact residual function, such as nephrectomy. An adequate urine collection is important to ensure a reliable calculation for this measure and can be done over the interdialytic interval. In children who are not yet toilet trained, such collections can be more problematic, but options such as weighing diapers can provide fairly accurate estimates.
- *T (dialysis time) and U (interdialytic interval):* Both of these variables are measured in minutes, and the actual duration of dialysis for the session in question rather than prescribed time should be used in case there was a disparity.

Along with the volume of distribution (V) and the urea generation rate (G), these variables can be used to calculate Kt/V. Because the times and clearances are either predetermined variables or are easily measured, these can be entered into the appropriate equations to generate V and G. As alluded to earlier, commercial software or Internet-based platforms or applications exist to perform these calculations. These resources greatly facilitate monitoring dialysis adequacy over time in large numbers of patients.

Common Errors in Calculations

As described previously, V is derived using serial measurements of BUN with respect to multiple HD sessions. Although there may be great variability in V between patients, V should remain fairly consistent for calculations on any individual patient. Thus, errors in calculations may be seen when V calculated for any given month or session varies greatly with respect to previous measurements. Common errors impacting the estimate of V include the following.

- *T is misreported:* The duration of the HD session is actually shorter or longer than that prescribed or utilized for the equation.
- *K is erroneous:* The blood flow (Q_B) actually delivered for the treatment being modeled is different than reported, often related to problems with dialysis access such as fistula or graft stenosis, clotting, or recirculation.
- *Measured BUN is wrong:* Either pre- or post-BUN samples are erroneous, generally related to incorrect timing of the samples or incorrect technique obtaining the samples.

Application of Urea Kinetic Modeling

Urea kinetic modeling can provide data about the estimated adequacy of HD and nutrition. Although the data can then be used to adjust the dialysis prescription or the child's dietary intake, it must be remembered that the calculated Kt/V is only an estimate of adequacy and that Kt/V within the target range may not necessarily denote optimal dialysis for all children. As with many therapies in children, a better overall measurement of dialysis adequacy would be consideration of the child's composite health, growth, and development while the therapy is ongoing. Guidelines from the British Society of Paediatric Nephrology eloquently describe dialysis adequacy as a "global concept that includes the clinical assessment of general well-being, nutrition, the impact on the patient's quality of life, anaemia, blood pressure, and fluid status as well as measures of clearance of putative uraemic toxins by the dialysis process."[6]

Unfortunately, given the need to adjust HD treatments over short spans of time, such long-term global measures of adequacy become supplemental to more immediate assessments such as Kt/V or PCR calculations. The data, nonetheless, can be quite useful in approaching and altering a patient's dialysis care.

For instance, a child found to have a PCR equal to their protein intake would be in neutral nitrogen balance. For an adult, this balance might be acceptable, but for a growing child, it would impact somatic growth and represent nutritional deficiency. Conversely, a child found with what

appears to be high predialysis BUN levels could have high dietary protein intake or may be inadequately dialyzed from previous sessions. In this case, assessing the PCR and Kt/V would differentiate between these situations. Whereas a high PCR could be modified by decreasing the protein intake to a more appropriate level, a low Kt/V could be adjusted by increasing the dialysis time, increasing the blood flow, or assessing the patient's access for technical complications.

National Kidney Foundation Kidney Disease Outcomes Quality Initiative Pediatric Recommendations for Dialysis Adequacy

The 2006 NKF KDOQI recommendations provide some guidance in assessing the adequacy of dialysis delivered to children.[3] Disappointingly, the 2015 KDOQI update makes no mention of children in their guidelines.[7] The 2006 report suggests that the delivered dose of dialysis should be measured routinely by formal urea kinetic modeling using a single-pool model.[3] The dose of dialysis (Kt/V) should accurately describe the fractional clearance of urea corrected for volume of distribution. These guidelines apply to children with a residual glomerular filtration rate below 15 mL/min/1.73 m^2 on a chronic HD regimen of three treatments weekly. The recommendations do not apply to children receiving dialysis at a different frequency or children with greater residual renal function in whom a standardized Kt/V would need to be used to assess adequacy. In addition, these recommendations do not apply to children with acute kidney injury receiving dialysis or children who are acutely ill and hospitalized receiving dialysis.

The NKF KDOQI guidelines specify that the minimum Kt/V should be 1.2 based on uncontrolled and retrospective reports that point toward improved patient survival with dialysis doses up to Kt/V of 1.2. There have, however, been a number of studies of the dose of HD as a predictor of outcome in children. One small study of prepubertal and early-pubertal children demonstrated improved growth with a Kt/V of 2.0 in combination with protein intake >150% recommended for children on dialysis.[8] In a group of four adolescents treated with HD 6 times a week, in spite of improvements in Kt/V, no change was seen in PCR or health-related quality of life scores over the 16-week span of the study, although blood pressures did improve.[9] However, a cohort of 16 children and adolescents receiving nocturnal HD thrice weekly demonstrated improvements in multiple parameters of ESRD management, including levels of PCR, albumin, weight, phosphorus, parathyroid hormone, blood pressure control, and quality of life.[10] Using data from the CMS ESRD Clinical Performance Measures Project, a study of adolescents receiving HD assessed mortality and hospitalization rates and found that teens with Kt/V <1.2 had higher hospitalization rates than those with Kt/V of 1.2–1.4, while those who had >1.4 had no added benefit in optimizing outcomes. The difference in mortality between those with Kt/V <1.2 (4.4 deaths/100 patient-years) and those with at least 1.2 (1.5 deaths/100 patient-years) was numerically but not statistically significant, although the total numbers of deaths in the cohort were low (14 deaths among 613 adolescents).[11]

The 2015 NKF KDOQI adequacy guidelines suggest that, to account for variability between prescribed and delivered dialysis doses, the prescribed Kt/V be 1.4 to ensure that a Kt/V of at least 1.2 is delivered.[7] Moreover, the guidelines stipulate that blood sampling be done precisely and in a consistent fashion to minimize recirculation or urea rebound and that the same methodology should be used for all applicable patients in any single dialysis unit to facilitate equivalent levels of care.

These guidelines have been promulgated with the understanding that they may not represent optimal dialysis but are serving as benchmarks for minimal dialysis dose delivery. Especially in children with the added physiologic burden of ongoing growth and development, it has been a consensus expert opinion that the delivered dose of dialysis should at least meet these standards. In fact, because achieving higher levels of Kt/V is often easier to reach in small children with lower volumes of distribution than large adults, many pediatric HD patients routinely achieve higher Kt/V levels, with only limited evidence that targeting these higher levels is of specific benefit.

Although not directed toward children per se, the 2015 guidelines address dialysis adequacy in those patients receiving more intensive HD, namely, exceeding thrice-weekly schedules. They recommend targeting a standardized Kt/V of 2.3 with a goal of a minimum delivered dose of 2.1. A standardized Kt/V of at least 2.0 in children receiving intensive HD correlates with a single-pool Kt/V of at least 1.2 measured in children receiving thrice-weekly HD.[12]

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Alternate Hemodialysis Prescriptions in Children

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The life span of a child on dialysis is 40 to 60 years less than that of the general population, but that of a pediatric transplant recipient is 20 to 30 years less than the general population. There is no doubt that dialysis is a significant risk factor for mortality and morbidity in children and adults alike. However, over the past decade, there has been a growing consensus of opinion recognizing intensified hemodialysis (HD) regimens, set either in a hospital or at home, as a viable, safe, and beneficial therapeutic option in children.

What Is the Optimal Dialysis Dose?

In the Hemodialysis (HEMO) Study comparing high-dose HD versus standard-dose HD, the relative risk of death was 0.96. In a secondary analysis, the HD dose showed a significant correlation with body mass index (BMI) and mortality. This raised the possibility of a survival advantage from increasing HD dose in low-BMI patients such as children.

The Dialysis Outcomes and Practical Pattern Study (DOPPS) review of 22,000 adult HD patients from seven countries found that a higher dialysis dose was an independent predictor of lower mortality on HD with a synergistic survival advantage with treatment time. Therefore, survival was most pronounced by combining a higher Kt/V with a longer treatment time, such that for every 30 minutes longer on HD, the relative risk of mortality was reduced by 7%. An Australian and New Zealand Dialysis and Transplantation (ANZDATA) analysis of 4193 patients found that the optimal dialysis dose for survival was a Kt/V greater than or equal to 1.3 and a dialysis session greater than or equal to 4.5 hours.

Such research set the scene for "quotidian" dialysis programs, namely a move away from conventional 4-hour, three-times-per-week dialysis to more frequent or more prolonged dialysis sessions, on the whole, located at home.

Adult Quotidian Hemodialysis Experience

The adult literature on quotidian dialysis practices is consistently positive. Compared with conventional dialysis, increasing frequency, time, or convective clearance is beneficial to the patient. For patients switching to short-daily HD, 33% survived at 6 years and demonstrated reduced hospitalization, fewer vascular access problems, reduced antihypertensive medication burden, lower incidence of left ventricular hypertrophy, improved anemia control, and a reduction in the use of phosphate binders as a consequence of the improved phosphorous clearance.

Nocturnal HD offers superiority over all other quotidian dialysis regimens. It is associated with a significant reduction in the risk for mortality or major morbid events compared with conventional HD. During a matched cohort study comparing survival between nocturnal HD and deceased and living donor kidney transplantation, there was no difference in the adjusted survival between nocturnal HD and deceased donor renal transplantation. The proportion of deaths among the three was 14.7% for nocturnal HD, 14.3% for deceased donor transplantation, and 8.5% for live donor transplantation. This is very reassuring for patients who are not eligible for transplantation or those waiting for a transplant. In a comparison with peritoneal dialysis (PD), patients reported a similar perception of control over their kidney disease and did not consider home HD as a more intrusive treatment.

Some adult units wishing to build on the success of extended HD prescriptions at home have started a wider range of in-hospital HD prescriptions. Graham-Brown et al. have shown improved plasma phosphate levels, left ventricle (LV) mass and favorable LV remodeling, reduction in dialysis-related symptoms, and sleep quality in adults on thrice-weekly, nocturnal HD, in-center compared to adult patients on conventional HD.

Pediatric Quotidian Hemodialysis Experience

Literature on pediatric quotidian HD is scarce and largely single-center home HD experiences. In-center quotidian prescriptions are often short-term, forming a bridging

therapy to home HD. Available results are similar to adult data and include pertinent pediatric-specific metrics, such as growth.

Tom et al. demonstrated improved growth in children without the requirement for growth hormone by dialyzing for 5 hours, three times per week, to yield a single pool Kt/V of 2.0 in combination with a caloric intake at 150% of the recommended daily allowance for age. Goldstein et al. delivered six-times-weekly HD at home using the NxStage system in four patients for 16 weeks. All of the children demonstrated progressive reductions in blood pressure (BP) load with concomitant discontinuation of antihypertensive medications in two patients. Serum phosphate levels improved without changes in phosphorus binder medication requirement.

Simonsen et al. first described the outcomes for nocturnal HD in four children aged 10 to 19 years who were treated with HD for 7 to 8 hours, 6 nights each week, for a period of 5 to 55 months. Achieving a weekly Kt/V of 7.2 to 13.6, these children had no fluid or dietary restrictions and required phosphate supplements to avoid hypophosphatemia. Catch-up growth was achieved, and quality of life improved markedly. Subsequently, Geary et al. reported on six children aged 11 to 17 years on nocturnal home HD. One patient developed a fistula aneurysm from repeated use in the absence of steal syndrome, and no line disconnections were reported. BP control was variable, with two patients with native kidneys still requiring antihypertensives, and three patients became hypotensive, requiring prophylactic midodrine to support their BP during ultrafiltration (UF). All patients were completely free from fluid and dietary restrictions, phosphate binders were discontinued, and all patients required supplementation with phosphate in the dialysate in combination with a higher calcium dialysate to prevent a net negative calcium balance. Appetite, well-being, school attendance, and physical and psychological health-related quality of life scores improved in all patients. However, caregivers' feedback did highlight the perceived "burden" of dialyzing at home. Many reflected on the increased intensity of workload that necessitated establishing a new routine within the home. The additional responsibilities evoked anxiety. The mother of one patient was psychologically and emotionally worn out after 1 year and moved to a hybrid program when the patient refused to revert back to in-center dialysis.

Perhaps one of the most exciting promises of extended home HD prescriptions is the ability to influence the outcomes and prognosis of a child positively. We describe the case of a 10-year-old with presumed severe, irreversible cardiomyopathy whose cardiac function normalized after 6 months of extended home HD.

Infrastructure

In a cost analysis of daily home nocturnal HD compared with conventional in-center HD, a 27% saving was seen for each patient dialyzed at home despite the increased "disposable" costs of more frequent dialysis sessions. However, this needs to be balanced against the resource commitment of providing safe and effective home therapy. It requires careful planning, resources, dedicated staff, and an appreciation of risk and governance issues. Programs need to decide on the type of dialysis offered, for example, nocturnal versus short daily treatments, long daily treatments, or hybrid prescriptions. They also need to decide on the type of dialysis machine and water source.

Finances

In pediatrics, diverting care from in-center dialysis beds to the patient's home results in significant savings because of the high staffing costs needed to deliver the 1:1 or 1:2 nurse-to-patient ratio. This needs to be offset against the initial setup cost to purchase or lease a dedicated dialysis machine for each patient; ideally, to adapt or convert existing rooms or structures into an appropriate training facility and employ a dedicated home HD team.

Staffing and Around-the-Clock Support

Home HD remains a relatively new therapy that places a high clinical risk activity in the community directly under the care of parents or other caregivers and patients. It is crucial to recruit a multidisciplinary team to support the families and to manage this risk. The composition of the team will vary depending on resources but, at a minimum, should include an HD nurse, dialysis technician, nephrologist, dietitian, and social worker. The inclusion of other allied health professionals such as a pharmacist, psychologist, community nurses, local pediatricians, and general practitioner is desirable for optimal support. In addition, it is absolutely essential to have a clear out-of-office communication pathway and after-hours policy to address families' urgent medical and technical queries while they dialyze their children at home in the evening, on weekends, and at night. To empower and support families further, we recommend providing them with written guidelines of normal ranges for a number of dialysis and physiologic parameters, with clear instructions on how to proceed if parameters fall out of the normal range.

Follow-up is dictated somewhat by geography and medical stability, but when in the community, patients should return to the clinic regularly, every 4 to 8 weeks. Between clinics, patients should receive regular phone or email reviews by the nurse specialist.

Training and Education

In principle, home HD should be offered as an equal dialysis option when discussing care pathways with appropriate families. However, before committing to home therapy, a home assessment needs to be completed. At the time of finalizing suitable training dates, advise the family that a continuous 4- to 6-week time commitment will be necessary.

Ideally, we recommend training two people at the outset. We also endorse training or involving the young adult patient immediately, thus promoting independence. Younger children should also be encouraged to learn about the machine setup, access, and dialysis prescription. All families should be offered repeated opportunities to enhance their knowledge and skills after they are home.

Companies supplying the dialysis equipment will often provide considerable teaching materials and expertise. However, in our experience, significant adaptation is often necessary for it to become both safe and relevant to the pediatric population.

Within our center, training is initially started in the HD unit. This is a safety precaution that allows us to rapidly detect and manage acute complications, such as a dialyzer reaction. Ideally thereafter, training should move quickly to a "family step-down" training facility, co-located within hospital grounds but separate from the dialysis unit, set up to simulate the home environment. If such a facility is not available, training should continue in the regular HD unit, stepping down directly to the patient's home with a higher number of home-assisted or -supported dialysis sessions with the home HD nursing team.

At the end of the training period, the trainee's competency needs to be formally assessed and signed off by the home HD nurse specialist. Within our unit, we also mandate that three or four dialysis treatments are completed unsupervised before discharge, with at least one-weekend treatment with no home HD staff on site within the hospital. In an attempt to improve adherence, we also ask the patient and their family to sign a treatment contract. After discharge, one of the home HD nursing team travels to the family home for the first dialysis treatment. In addition to providing onsite support, this can also provide an excellent opportunity to engage with the community teams.

Retraining opportunities are offered, at minimum, every 6 months or are mandated after an adverse event, change in treatment, or dialysis access such as switching from central lines to arteriovenous fistulas.

Remote monitoring is not universally used, but if available, it may alleviate some patient or parental anxieties. Pediatric programs typically use an existing adult facility, given the small numbers. Remote monitoring initially required a dedicated phone line and modem, but wireless technology is supplanting this.

Dialysis Equipment

Dialysis Systems Requiring Home Water Conversions

A majority of HD machines that are suitable for home HD require home water conversions in order to produce the large volumes of high-quality dialysate necessary for dialysis treatment. This cost can sometimes become a barrier to delivering home HD in children when transplantation is the preferred renal replacement therapy, and dialysis is viewed as a temporary interim measure. On average, home HD with water conversion is more cost effective than in-center HD if patients stay on dialysis for more than 14 months to offset training and setup costs.

Water conversion requires the installation of a cold water outlet and a drain to allow the carbon filter, reverse osmosis unit, and dialysis machine to be fitted. A system for testing the water quality needs to be put in place. Typically, families test their water for chloride every session and bring a sample for advanced testing to their monthly hospital clinic visits. The dialysis technician will test for chemicals, endotoxins, and microbiology.

Water conversions, although necessary, can be a source of additional work and anxiety for families because complications such as leaks and blocked drains can occur and need to be addressed as a matter of urgency.

Mobile Hemodialysis System: NxStage

The NxStage System One is a portable home dialysis machine that functions without home water modifications. Dialysate is prepared at home using the NxStage PureFlow SL integrated water purification and dialysate production system. Purified water is produced in 40- to 60-L batches from the ordinary tap and mixed with sterile-filtered concentrate to produce Association for the Advancement of Medical Instrumentation (AAMI) quality, lactate-buffered dialysate. Alternatively, dialysis could be delivered using preprepared 5-L sterile dialysate bags. At Great Ormond Street Hospital, we currently use three NxStage dialysis circuits in the home environment. The first is their standard circuit, CAR-172-C, which is used in children weighing 25 kg or more. This circuit has a preattached polysulfone dialyzer that was associated with a significant dialyzer-induced thrombocytopenia in 40% to 60% of our children. These children are now successfully dialyzed at home with the CAR-124-C, a modified continuous venovenous hemofiltration circuit, with a smaller extracorporeal volume that can house an alternative, appropriately sized dialyzer and is suitable for children weighing 20 kg or more. Finally, we have adapted another continuous renal replacement therapy circuit, CAR-125-B, which with an appropriately sized dialyzer, can treat children weighing 10 kg or more.

Prescribing dialysis treatment using the NxStage system is very different from standard HD prescriptions because the former relies on the principle of efficient use of dialysate, with the spent dialysate being highly saturated. The flow fraction is the ratio of effluent flow (spent dialysate plus UF) divided by blood flow rate and corresponds to the degree of dialysate saturation. When the dialysate saturation approaches 100%, the treatment dose is approximately equivalent to the volume of dialysate used per session. With flow fractions between 30% and 35%, clearance of small molecules, such as urea, is very efficient in achieving dialysate saturation of 90% to 95%. As flow fraction increases, clearance falls but to a greater proportion in larger

molecules such as creatinine. Therefore, one has to strike a balance between dialysis time, blood flow rates, and flow fraction to preserve dialysate efficiency and both small- and middle-molecule clearance. We typically start with a flow fraction of 35% to 40%, dialyzing for 5 hours four times a week with a dialysate volume of 70% to 80% of the estimated total body water volume per dialysis session.

Patient Selection

As a result of our growing confidence and experiences with home HD, we now have no fixed or absolute patient criteria for home HD except for a commitment to dialyze at home. The referral could be initiated for a number of reasons, including medical, social, educational, or simply patients exercising their rights to choose. Psychosocial involvement may be necessary to ensure families' suitability for home therapies and support them in their decision. Self-care within the HD unit often facilitates the transition to home dialysis by allowing patients and families to build their confidence gradually. We also believe that failed home PD does not preclude the possibility of home HD.

Suggested criteria for accepting patients into a home HD program is listed here. However, specifics may vary among programs.

- Commitment to dialyzing at home. A trained caregiver is not a prerequisite for young adults 16 years of age and older.
- Patient weight 10 kg and above (determined by the combined volume of the extracorporeal circuit and dialyzer).
- Well-functioning vascular access.
- No psychosocial concerns that cannot be managed in the community.
- Home of a sufficient size to accommodate the dialysis equipment and a month's supply of dialysis consumables.
- In consideration of the reverse osmosis dialysis systems at home, the ability to modify the water source.
- Family household hygiene that does not compromise the patient's risk of infection.
- Child does not live in an area with frequent and prolonged disruptions to electricity supplies. An emergency source of power must be available at all times.

Prescriptions

In our experience, one of the key drivers for families to agree to home HD is the flexibility to perform the HD treatment around their own schedule. The impetus for clinical teams is in improving patient outcomes and quality of life. Attempts to achieve both goals with one dialysis prescription can be difficult, but some useful guides do exist.

Frequent daily dialysis prescriptions typically comprise 2 to 3 hours of dialysis six to seven times per week. Such prescriptions are very useful for working parents who cannot start dialysis until late in the evening or need to complete treatments early in the evening because of evening work shifts. Such regimens seldom give complete freedom from phosphate binders but can be useful in young children who cannot tolerate long dialysis sessions, in patients on parenteral nutrition or gastrostomy feeds, and for patients who do not tolerate aggressive UF or are not optimally compliant with fluid restrictions. Of all the home dialysis regimes, high-frequency prescriptions are the most expensive in line with the higher dialysis consumables cost.

Alternate-day, prolonged 5- to 6-hour dialysis sessions, typically in the evening, eliminate fluid restrictions and liberalize dietary and phosphate restrictions. Alternate-day therapy frees up more time for the patient and caregiver for social or recreational activities. Such treatments are also associated with an improved sense of well-being. This can come at a cost, especially in young adults, who can become increasingly frustrated about sacrificing their evenings for HD.

Home nocturnal HD prescriptions are typically 8 hours overnight, daily, or on alternate nights. Gentler dialysis prescriptions will virtually eliminate adverse intradialytic symptoms and offer superior clearance of "uremic toxins," particularly phosphate and middle molecules. However, owing to the nonselective nature of HD purification, essential plasma components are also removed, resulting in a theoretical risk of deficiencies. Patients usually have complete freedom from dietary and fluid restrictions, and phosphate binders can be withdrawn, resulting in a reduced medication burden. In patients dialyzing daily, hypophosphatemia is common and can be treated by oral supplements or by adding phosphate to the acid dialysate concentrate as a sodium phosphate (Fleet) enema. Higher dialysate calcium levels of 1.75 mmol/L are recommended from the outset to protect against a negative calcium balance. Some patients may develop persistently low BP, necessitating prophylactic midodrine at the start of dialysis to support the BP, thus allowing UF and reducing the risk of the circuit clotting.

Dialyzing overnight can induce anxiety in both caregivers and children because of fears of disconnection or not hearing machine alarms. Some units have advocated equipping the dialysis machine with a port for downloading treatment data onto a central remote monitoring station via a personal computer or modem. We recommend a baby monitor to amplify the sound of the alarms overnight. Access monitoring is highly recommended using either enuresis alarm pads or more sophisticated monitors such as Hemodialert that are sensitive to fluid and the color red. A cycler base fluid detector that alarms if there are any leaks within the circuit can also be used.

Dialysis Adequacy

Traditionally, dialysis adequacy is assessed by urea clearance quantified as urea reduction ratio or single-pool or equilibrated Kt/V. We believe this is an oversimplification, and

the success of a dialysis regimen should be assessed through the combined outcomes of several important endpoints such as cardiovascular health, quality of life, and growth, to name a few. Based on current technology and practices, it is not unrealistic to aim for adequate growth, control of anemia, optimal BP and control of bone and mineral disorders, absence of left ventricular hypertrophy, and excellent psychosocial health.

Conclusion

HD is necessary for many children with end-stage renal disease, but outcomes are extremely variable. Quotidian dialysis programs at home are producing results never anticipated in dialysis patients, and even though data are scarce in children, the projected and demonstrable benefits are hard to ignore. We as a pediatric nephrology community have a responsibility to promote, educate, and actively recruit patients into quotidian dialysis programs, based in a hospital or at home to allow a greater proportion of children to receive the therapeutic benefits.

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Anticoagulation in Children Undergoing Hemodialysis, Continuous Renal Replacement Therapy, or Apheresis Therapy

MARTIN KREUZER, MD • DIETER HAFFNER, MD

Introduction

Extracorporeal blood purification techniques are associated with clotting of the extracorporeal circuit; therefore, with the exception of some coagulation disorders, anticoagulation is mandatory. In pediatric practice, the relative surface area of the extracorporeal circuit is increased in relation to its blood volume. The use of smaller lumen diameter lines provides greater surface contact. Passage of blood through the extracorporeal circuit results in activation of leukocytes, macrophages, lymphocytes, platelets, and the complement cascade. Monocyte activation, especially in the presence of activated platelets, results in surface expression and local release of tissue factor, thus activating the coagulation cascade promoting thrombosis in the extracorporeal circuit. In pediatric patients, smaller lumen in catheter, needle, and circuit tubing results in higher resistance, more turbulent flow, and limited blood flow rates compared with adults. The type of blood purification technique has implications for the choice, use, and handling of anticoagulants. In intermittent hemodialysis (HD), anticoagulants are needed for only about 4 hours to prevent the circuit from clotting. In patients undergoing continuous renal replacement therapy (CRRT) procedures, the need for and potential risks of anticoagulants are present for a considerably longer period of time. Most commonly, clotting affects small filters, and their lifetime in CRRT is significantly shorter as compared to larger filters regardless of the type of the anticoagulant.

General Considerations

In pediatric practice, most centers use unfractionated heparin (UFH) for treatment in patients without increased risk of hemorrhagic complications because it is inexpensive and easy to handle. Some centers use low-molecular-weight heparins (LMWHs) instead for better predictability.

In patients with heparin-induced thrombocytopenia (HIT) type II (and children with type I), alternatives to heparins are recommended. In noncritically ill children with HIT, we favor argatroban, a reversible direct thrombin inhibitor (DIT) with a considerably short half-life and only a few adverse effects.

Data from adults as well as children strongly indicate regional citrate anticoagulation in patients who are actively bleeding or at risk of bleeding (e.g., within 3 days of a bleeding episode, a surgical wound, accidental wound, or tonsillectomy within the past week, or < 2 weeks from a cerebral or retinal hemorrhage).

Long-term anticoagulation in CRRT needs strict anticoagulation management and frequent anticoagulation monitoring, especially in critically ill children.

Very small children (< 10 kg body weight) need stringent anticoagulation monitoring. Because of a very slow blood flow and smaller lumen lining, they need higher anticoagulant dosing and, thus, have an increased risk of hemorrhagic complications.

Unfractionated Heparin

The anticoagulant most commonly used is UFH. It consists of a large series of glycosaminoglycans, which interact with antithrombin. Although heparin effectively reduces coagulation cascade activation and thrombin formation, it can also directly activate platelets, which results in microthrombi deposits on the dialyzer wall.

For efficient use of heparin, antithrombin is needed. Heparin is an ineffective anticoagulant in patients with low plasma antithrombin levels (e.g., children with severe liver impairment or with an inborn antithrombin deficiency). If necessary, administer antithrombin to keep levels within a normal range.

Heparin is a systemic anticoagulant with an action time of 3 to 5 minutes. It is not removed by dialysis and only partially by plasma separation. About 35% is excreted via the kidney; therefore, the half-life is increased to 50 to 70 minutes in patients with acute kidney injury or end-stage renal disease. The disparity in half-life is greatest in the extremes of age and weight, especially in children weighing less than 10 kg. Heparin is a very negatively charged molecule that adheres well to plastics.

It is important to use a properly diluted heparin solution to prevent adherence of heparin only to the inner lining of the tube. Use a minimum heparin infusion velocity of 2.0 mL/h!

Heparin can be used in children without risk of bleeding. A loading dose of 25 to 50 IU/kg or 300 to 1000 IU/m^2 (maximum, 2000 IU) should be administered, followed by a maintenance dose of 10 to 30 IU/kg/h. Loading dose (or no loading dose) had no effect on the occurrence of hemorrhagic complications in children with increased bleeding risk (see the Regional Citrate Anticoagulation section). In intermittent HD, the infusion is discontinued some 30 minutes before the end of the dialysis, especially in children with shunts, to prevent excess bleeding from the puncture site.

Because there is variability between batches of UFH, bedside monitoring of its effects is crucial. Monitoring can be easily performed by using bedside whole-blood activated clotting time (ACT). ACT values significantly differ among various ACT monitoring systems (e.g., ACTester, iSTAT, Hemocron, ACT plus). ACT measurements should be performed in all patients before and while undergoing heparin therapy and tailored not only to the patient but also to the system used. For sufficient anticoagulation, ACT is aimed at 1.7- to 2.3-fold of pre heparin baseline. The activated partial thromboplastin time (aPTT) can be used but needs a laboratory test. The aim is a 1.7- to 2-fold of baseline or upper normal value. With every 10-second aPTT prolongation, the risk of bleeding complications is increased by 50%!

Although the introduction of heparin has been one of the major advances in the history of HD, its side effects can be significant. The most severe of these is bleeding. Heparin can cause allergic reactions because it is derived from pork or bovine intestine. Long-term treatment with heparin can cause osteoporosis, alopecia, and abnormal liver function test results and may promote hyperkalemia (by antagonizing aldosterone).

In case of severe bleeding complications, heparin activity can be quickly reversed: Use 1 mg protamine for every 100 IU of heparin.

Occasionally, patients can develop HIT. The more severe (antibody-mediated) type II reaction usually develops when the patient has been exposed to large doses of heparin. Type II can be observed in 2% to 3% of patients about 5 to 10 days after exposure by a significantly decreased thrombocyte count (< 50,000/µL). Instant withdrawal of heparin in type II of HIT is mandatory. Generally, in children with HIT, alternatives to UFH should be used for anticoagulation.

On dialysis, the need for a significantly increasing heparin dosage to achieve sufficient anticoagulation can be a clue to subclinical HIT (type I). Thrombocyte count can be normal or only slightly decreased. In these cases, HIT should be checked.

Low-Molecular-Weight Heparins

LMWHs were developed to improve the predictability of anticoagulant effects by cleavage of UFH. They are not a single entity, so they vary in their relative effects on inhibiting factors IIa and Xa.

Compared with UFH, LMWH showed no significant difference in terms of bleeding, vascular compression time, or thrombosis in meta-analyses.

LMWHs are mostly cleared by the kidneys. So their half-life is considerably prolonged in renal failure (with enoxaparin having the longest with about 28 hours), and they are not an option for short-term dialysis or apheresis sessions (< 4 hours). In addition, they tend to accumulate in patients undergoing daily dialysis (e.g., small children). For CRRT, they may be beneficial. They are, in general, administered as one dose at the start of dialysis (for dosage, see Table 74.1). The dosage depends on the LMWH used as well as on frequency and duration of HD sessions. A single bolus may not always provide sufficient anticoagulation for a very long dialysis session (e.g., overnight dialysis or CRRT). Some proportion of the LMWH bolus may be lost via the filter because of its lower molecular weight compared with UFH. Coating the dialyzer surface with vitamin E reduces the loss and may lead to dose reduction.

Monitoring the effectiveness (and risk) of LMWH is one of the major drawbacks to its use. Because of an only modest effect on thrombin, only anti-Xa activity can be monitored. Peak levels of 0.4 to 0.6 IU/mL should be achieved as well as levels below 0.2 IU/mL at the end or soon after dialysis.

HIT may rarely develop with LMWH. Because of cross-reactions, LMWH should not be used in patients with a history of HIT type II. If bleeding does occur, it is mostly more severe compared with UFH. Because protamine has only a moderate effect on LMWH, fresh-frozen plasma (FFP) may be required in severe hemorrhagic complications.

TABLE 74.1 Pediatric Dosing Recommendations for Low-Molecular-Weight Heparins During a Standard 4-Hour Dialysis Session*

Anticoagulant	Half-Life* (h)	Pediatric Dose	Anticoagulation Target
Tinzaparin	4.5	50 IU/kg	Anti-factor Xa activity 0.2–0.4 (–0.6) IU/mL
Dalteparin	5	40 IU/kg	
		<15 kg: 1500 IU	
		15–30 kg: 2500 IU	
		30–50 kg: 5000 IU	
Reviparin	5	85 IU/kg	
Nadroparin	5	114 IU/kg	
Enoxaparin	27.7	24–36 mg/m^2	
		0.5–1.0 mg/kg	

*Note that half-lives vary with residual renal function.

Systemic Anticoagulants as Alternatives to Heparins

Proteoglycans or DIT should be used for anticoagulation in patients with HIT. Proteoglycans are naturally occurring anticoagulants produced by many species. In current clinical practice, danaparoid (a mixture of heparan sulfate, dermatan sulfate, and chondroitin) is the most commonly used proteoglycan for systemic anticoagulation. Predominantly, it performs an anticoagulant activity against factor Xa. Compared with other anticoagulants for treating patients with HIT, danaparoid has been reported to be more effective in preventing thrombosis by preventing activation of platelets by HIT type II antibodies. The main disadvantage of danaparoid is the long half-life of about 30 hours in kidney injury. Thus, monitoring and adjusting the loading dose should not only depend on anti-factor Xa activity at the end of the dialysis session but also on anti-Xa activity before the start of the subsequent dialysis session. Pediatric dosing recommendations are given in Table 74.2. About 20% of danaparoid is removed by HD and CRRT.

Bivalirudin is a recombinant form of the natural anticoagulant hirudin (from the medical leech). Bivalirudin in children with HIT is off-label use and pediatric dosing information for renal impairment does not exist. Therefore, we cannot recommend it. The comparable drug lepirudin is no longer commercially available.

Argatroban is a reversible DIT. It is a synthetic peptide derived from arginine. Argatroban is licensed by the Food and Drug Administration for the treatment of HIT in children in the United States. Patients are treated with a continuous infusion. Pediatric dosing recommendations are given in Table 74.2. Argatroban is mainly metabolized in the liver. The half-time is about 50 minutes. Because of protein binding (54%), argatroban is only partly removed by dialysis, and consideration should be given to reducing the dose toward the end of the dialysis session to prevent prolonged bleeding from the puncture site. Argatroban is highly selective for thrombin (circulating and fibrin bound). In contrast to the anticoagulants mentioned previously, there are no reports on antibody formation against argatroban. Again, there is no antidote, and in case of serious bleeding, FFP and activated factor VII concentrates are needed.

TABLE 74.2 Alternative Options to Heparin in Cases of Heparin-Induced Thrombocytopenia

Anticoagulant	Loading Dose	Maintenance Dose	Monitoring	Dose Adjustment
Danaparoid	1000 + 30 IU/kg for age younger than 10 years or 1500 + 30 IU/kg for age older than 10 years	None	Predialysis anti-Xa <0.30 IU/L	Reduce dose by 250 IU if predialysis anti-Xa >0.3 and <0.5 and stop if >0.5 IU/L.
Argatroban	—	0.7 µg/kg/min (liver disease, 0.2 µg/kg/min)	aPTTr target 2.0–2.5 check after 2 hours	Adjust if required by 0.25 µg/kg/min and recheck aPTTr.

aPTTr, Ratio of therapeutically prolonged activated partial thromboplastin time (aPTT) and baseline aPTT or normal value.

In critically ill children, the clearance of argatroban is significantly reduced by about 50% compared with healthy adults! Do not use argatroban in children with cholestasis because it is mainly secreted by bile and excreted with the feces.

Regional Anticoagulation with Citrate

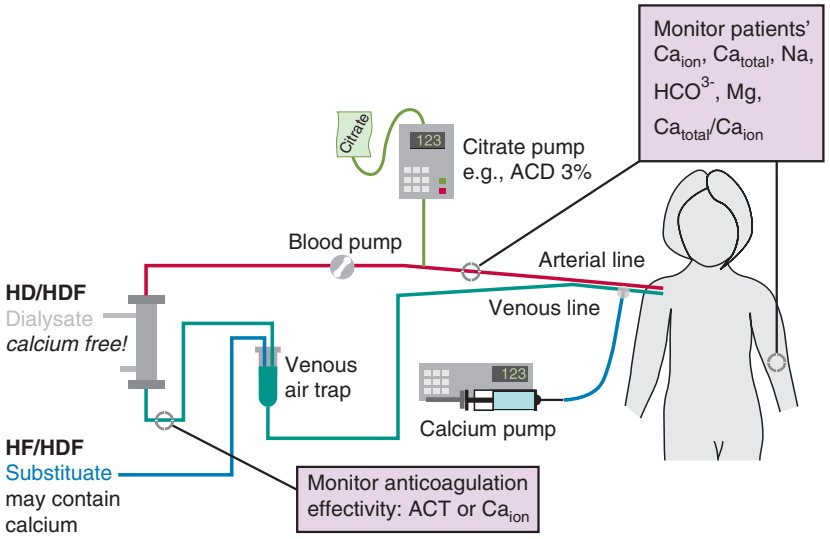
Citrate is a potent regional anticoagulant. It decreases free (ionized) serum calcium by forming chelate complexes. Thus, calcium is no longer available for the activation of tenase and prothrombinase complexes within the coagulation cascade. This effect is easily reversed by a calcium substitution. This mechanism provides the means for regional anticoagulation exclusively in the extracorporeal blood circuit.

Anticoagulation with citrate introduces a degree of complexity to the treatment. In any form of HD, a calcium-free dialysate is needed. If trisodium citrate is used, dialysate sodium concentration has to be decreased. Citrate has a half-life of only a few minutes and is mainly metabolized to bicarbonate in the liver (and skeletal muscles). Thus, during prolonged dialysis sessions, alkalosis may occur, and the bicarbonate level of the dialysis fluid has to be decreased. With modern dialysis machines used during intermittent HD, both sodium and bicarbonate levels of the dialysate can be easily adapted to accommodate these needs. For CCRT, commercial calcium-free fluids with reduced sodium and bicarbonate content are available.

Modern dialysis machines are fitted with a pump for citrate infusion controlled automatically by blood flow. If using *additional* pumps with the dialysis machine for infusion of citrate or calcium, be sure to have a stable blood flow and immediately pause the external pumps in case the blood pump stops. A significant citrate bolus injection into a central venous catheter immediately depletes ionized calcium within the ventricles and may result in sudden cardiac arrest.

The citrate infusion must be adjusted to the blood flow to achieve a postfilter ionized calcium concentration of 0.20–0.30 mmol/L (0.80–1.20 mg/dL) or an ACT prolongation 1.7-2.3-fold of baseline and prevent clotting within the circuit, which equates to a predialyzer citrate concentration of about 4–6 mmol/L (77–115 mg/dL). A 4% trisodium citrate (TSC 4%) and a 3% acid citrate dextrose (ACD) solution are available. We recommend using ACD solution, which is widely available for stabilizing blood products. With ACD solution, dosing in children is quite simple: Choose a prefilter infusion rate of the ACD solution (in milliliters per *hour*) that is two times the blood flow (in milliliters per *minute*) or an ACD to whole blood relationship of 1:26. This protocol can be used with HD, CRRT, and membrane-based apheresis procedures. Centrifuge-based apheresis requires more citrate, for example, an ACD to whole blood relationship of 1:12.

The effect of citrate is reversed by calcium infusion. Depending on the patient's situation (e.g., hypocalcemia in critically ill children) and the dialysis technique, recommendations on calcium substitution are not easy to provide. Using 10% calcium gluconate solution (with 0.23 mmol/L calcium or ~ 1.0 mg/dL), one should start the calcium solution (in milliliters per *hour*) with a quarter of blood flow (in milliliters per *minute*) or a relationship of 1:15. In continuous hemofiltration, the substitute usually contains calcium. Hence, an additional calcium substitution is needed only in one-third of the patients. Regional citrate anticoagulation in hemofiltration is only possible with a postfilter dilution technique (Fig. 74.1). Check the patient's ionized calcium level before dialysis. If it exceeds 1.30 mmol/L (5.20 mg/dL), start without calcium infusion, and begin substitution only if the patient's ionized calcium levels decrease below 1.10 mmol/L. If hypocalcemia is present (ionized calcium



• **Fig. 74.1** Regional citrate anticoagulation. *ACD*, Acid citrate dextrose; *ACT*, activated clotting time; *HD*, hemodialysis; *HDF*, hemodiafiltration; *HF*, hemofiltration.

< 1.00 mmol/L or 4.00 mg/dL) or with plasmapheresis using FFP (usually containing additional citrate), start with a much higher calcium infusion rate (e.g., double the amount mentioned earlier using a relationship to blood flow of 1:7.5). The aim is to keep the patient's ionized calcium levels within the physiologic range (1.00–1.30 mmol/L or 4.00–5.20 mg/dL).

Calcium substitution should never be connected to the venous air trap. Turbulence in blood flow and contact with air result in the immediate formation of clots.

Be aware that a perivascular leakage of calcium-containing solution will lead to severe tissue necrosis and damage!

Regional citrate anticoagulation is more complex compared with other anticoagulation techniques because not only does adequacy of anticoagulation need to be monitored (which can be by postdialyzer ACT) but also for patients' safety, several serum parameters have to be monitored, including ionized calcium level; the ratio of total calcium and ionized calcium (as a marker for citrate intoxication); and sodium, bicarbonate, and magnesium levels. We recommend monitoring postfilter ACT and patients' ionized calcium levels every 15 minutes within the first hour of initiation of treatment and hourly thereafter. The estimated volume load of the citrate and calcium solution has to be added to ultrafiltration anticipated to prevent hyperhydration if not adjusted automatically by the dialysis machine. With postfilter ionized calcium falling below 0.30 mmol/L (1.20 mg/dL), ACT acts nearly like an on-off switch. Thus, in contrast to heparin, one does not have to worry if postfilter ACT is endless in regional citrate anticoagulation. We just interrupt the testing process by the time ACT exceeds 300 seconds.

A total calcium-to-ionized calcium ratio greater than 2.4 has been associated with a more than 30-fold higher mortality rate in patients with regional citrate anticoagulation 4 weeks later. A ratio greater than 2.4 equals citrate intoxication! Discontinue citrate infusion.

Under normal circumstances, regional citrate anticoagulation is effective in intermittent HD for up to 5 hours. In the case of pediatric apheresis therapy, it is important to realize that the citrate and calcium solution fluid load can be substantial, and apheresis therapy does not provide the possibility of fluid removal. Consider using citrate formulations with higher citrate content (e.g., 14.7% = 0.5 M, or 35.3% = 1.2 M). In that case, the citrate dosing protocol (as earlier) has to be converted.

Citrate anticoagulation becomes more difficult with continuous procedures. Despite using solutions with reduced sodium and bicarbonate content over the period of CRRT with regional citrate anticoagulation, there may be an accumulation of sodium, bicarbonate, and sometimes citrate and total calcium. Sodium and bicarbonate accumulation can be handled with the use of a predilution 5% glucose solution. In more severe cases, the standard substitute solution in continuous hemofiltration can be replaced (partially or totally) by an infusion solution containing less sodium, alkali, or both.

Recent studies suggest that regional citrate anticoagulation for CRRT in pediatric patients with liver failure is safe and feasible. However, citrate toxicity, calcium imbalance, acidosis, and alkalosis were frequently observed, and in-hospital mortality was as high as 57% in one study. We still consider regional citrate anticoagulation as very challenging in small children with liver failure and in anhepatic children (e.g., the first days after liver transplantation).

Other Regional Anticoagulants

Prostacyclin is the most potent of the prostanoids, which are naturally occurring anticoagulants and have very short half-lives of only a couple of minutes. Prostanoids (especially prostacyclin) are also potent pulmonary and systemic vasodilators, which produce side effects. Flushing and hypotension are commonly observed side effects, and prostanoids should not be used in children with hemodynamic instability. The systemic side effects of prostacyclin can be significant! Hypotension can be avoided by ensuring patients are not hypovolemic and by infusing prostacyclin starting at a rate of 0.5 ng/kg/min before the start of dialysis and increasing the dose over a few minutes (aim for 5.0–10.0 ng/kg/min). Because the half-life is in minutes, any hypotensive episode can readily be reversed by stopping the infusion. Prostanoids mainly block platelet activation, so they do not have any measurable effect on standard laboratory coagulation assays. Therefore, measuring a coagulative effect and monitoring efficacy are not possible.

Nafamostat is a serine protease inhibitor that inhibits coagulation and fibrinolysis by inactivating thrombin, plasmin, trypsin, kallikrein, coagulation factors XIIa and Xa, and complement. It is not available in the United States and is used mainly in Japan and South Korea. Nafamostat has a half-life of 5 to 8 minutes. Nafamostat is started with no initial bolus as a continuous infusion (200 mg of nafamostat mesilate mixed with 20 mL of 5% dextrose solution) at a rate of 0.25 mg/kg/h. The infusion rate is then adjusted according to circuit ACT. Nafamostat causes acute liver failure in a child, and clinical data is very limited.

Oral Anticoagulants

A pilot study with 17 patients recently showed that vitamin K antagonists in children on chronic HD improved central venous catheter survival without major hemorrhagic complications. Due to a variety of safe and feasible alternatives for HD anticoagulation, we cannot recommend vitamin K antagonists. However, they may be useful in rare individual cases (e.g., children with inborn hypercoagulopathies in need of permanent anticoagulation). Other oral anticoagulants, such as fondaparinux, apixaban, edoxaban, rivaroxaban, or dabigatran, are not recommended for children with impaired kidney function.

Central Venous Line Locks and Treatment of Clotted Catheters

In most centers, central venous lines are locked with UFH, either neat or diluted to 1000 to 2500 IU/mL. The lock places the patient at an increased risk of bleeding because of systemic infusion of part of the anticoagulant. Thus, undiluted heparin cannot be recommended in children. An accidental flushing of the locked catheter may cause a serious hemorrhagic complication.

Citrate has become a potent alternative as a catheter locking agent. A 5% sodium citrate lock is equally efficient in preventing catheter dysfunction as a 10% citrate lock. In a higher concentration (30%), it may also prevent bacterial growth and biofilm deposition. In contrast to heparin, it is not a problem to slowly flush the lock if the line cannot be aspirated.

In patients with hypercoagulability, a heparin or citrate lock alone may not be sufficient to maintain catheter patency. A regular instillation of urokinase or tissue plasminogen activator (tPa) once a week or every fortnight is helpful in preventing catheter clotting. Clotted catheters can regain patency with urokinase (5000 IU/mL) or tPa (1 mg/mL). Some patients undergoing intermittent HD may need LMWH (enoxaparin 0.1–0.5 mg/kg) administered subcutaneously on days without dialysis to prevent clot formation at or within the catheter. Because of a prolonged half-life of LMWHs in kidney injury, monitoring anti-Xa activity (aim > 0.6 IU/L) before dialysis is necessary.

Recommended Reading

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Prescribing Peritoneal Dialysis in Children

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Peritoneal dialysis (PD) became a more available therapy for children in the 1960s, such that it was no longer considered "experimental" by the early 1970s. Further advances have been made in the size of catheters and tubing and the technology of automated cyclers, which has made PD more adaptable to a variety of patient needs. This would seem to make PD a potentially optimal modality for children with end-stage renal disease (ESRD) requiring dialysis, as they have different primary etiologies of renal disease, come in different sizes, and have different daily treatment demands. However, despite this relative indication of its use in children, the percentage of pediatric dialysis patients on PD seems to be decreasing in the United States. This chapter hopes to set a framework of considerations when discussing PD as a potential modality of renal replacement therapy for children.

Initiation of Dialysis in Children

Indications for initiating renal replacement therapy in children are based on clinical, biochemical, and psychosocial parameters, which should be individualized for each patient. These parameters may vary based on the child's age, as both the biochemical norms and the developmental needs of the child can change, as well as their primary etiology of chronic kidney disease (CKD). An infant with renal dysplasia and a serum phosphorus level of 6 mg/dL is desirable, but if they are not gaining weight, it can be very worrisome. Whereas an adolescent with lupus nephritis would benefit from lower phosphorus levels, while weight gain may put them at certain cardiovascular risk. Inappropriate nutrition in children may allow for "normal" laboratory results (e.g., potassium, urea) and manifest not with weight loss but with growth failure. Therefore, a regular global assessment of the child with advanced CKD, with particular attention to growth and development, is warranted.

Objective criteria for initiation of dialysis in children have been iterated in the most recent Kidney Diseases Outcomes Quality Initiative (KDOQI) guidelines on PD adequacy. Those recommendations are that dialysis initiation should be considered in the pediatric patient when their estimated glomerular filtration rate (GFR) is ≤ 15 mL/min/1.73 m^2 and recommended in the pediatric patient with a GFR ≤ 8 mL/min/1.73 m^2. European guidelines have shared this objective threshold of considering dialysis if the GFR is ≤ 15 mL/min/1.73 m^2. Recent reports have shown that the percentage of pediatric patients initiating dialysis at higher estimated GFR (> 10) had increased 2.5-fold in the United States over the past two decades, from 16.5% in 1995 to 40.8% in 2015. A comparison of those initiating dialysis at a higher GFR (> 10) to those at a lower GFR (< 10) revealed a 24% higher risk of death for those initiating at the higher GFR cut-off after censoring patients upon being transplanted. However, there was not a statistically significant difference in mortality risk seen among PD patients who initiated dialysis at the higher GFR cut-off compared to the lower GFR. A similar study performed in Europe comparing children who initiated dialysis at a higher estimated GFR (> 8) found no clinically relevant benefit in terms of overall survival, growth, or access to transplantation, but again no separate distinction was made for those initiating PD at the different GFR thresholds. Therefore, there does not seem to be an absolute threshold of GFR in children at which dialysis, or PD, needs to be initiated, although experts would suggest consideration once estimated GFR is < 10 mL/min/1.73 m^2.

However, both North American and European guidelines recommend that the pediatric patient's clinical course takes precedence over any estimate of kidney function. Initiation of dialysis should be considered at higher GFR levels if the patient has findings or symptoms that are refractory to medication or dietary management. Similarly, dialysis does not have to be automatically started at lower GFR levels if the patient has normal lab values and is otherwise asymptomatic. Metabolic disturbances seen in pediatric patients include hyperkalemia, hyperphosphatemia, metabolic acidosis, and azotemia, although normal serum values for potassium are slightly higher for infants and normal values for phosphorus are higher for preadolescents. The clinical

findings may include fluid overload, hypertension, malnutrition, and growth failure. As there is a preponderance of nonglomerular disorders causing ESRD in children, urine output may be preserved, while fluid overload and hypertension, which is almost universally seen in adults with ESRD, may not even occur in some pediatric patients. Growth failure in children can be particularly difficult to detect if not cognizant of its findings. It may manifest with a static weight during a period when a child would normally be gaining or a decrease in height velocity, a measure unique to children which varies greatly by growth stage. Other symptoms of ESRD in children may include anorexia, nausea, vomiting, and decreased energy levels. Frank's neurologic symptoms of uremia are rare in children but may present with more subtlety, such as decreased levels of concentration and attentiveness. Diminished school performance or decreased daily activity levels should be screened for and considered as pertinent findings of disease management.

Similar to KDOQI recommendations in adults with CKD, patient and/or caregiver education about renal replacement therapy options should occur as the patient advances into stage 4 CKD. The timing of education should ideally give the patient and caregivers ample time to decide upon a dialysis modality, if needed, and for any advanced access planning. This should include anticipatory planning for other surgeries that may be needed in the pediatric patient, such as feeding tube placement, native nephrectomy, or major urologic procedures. The education should be conducted by a multidisciplinary team, including dialysis nurses, social workers, and dieticians, all of whom should also assess the patient and caregiver's comprehension of the risks, benefits, and demands of the available treatment options. The education should present nonbiased information on hemodialysis (HD), PD, and transplant to the patient and family, but unavoidably may be influenced by the experiences of the multidisciplinary team.

Factors to Consider in Modality Choice in Children

When evaluating the dialysis modality options for pediatric patients, it is important to weigh both the medical and social needs of the individual patient. The most recent KDOQI recommendations on dialysis adequacy conspicuously did not list any indications or contraindications for PD in adults, unlike previous versions. However, in the pediatric recommendations, there are still some patients for whom PD is clearly indicated (see Table 75.1). Infants and small children can be especially prone to vascular access complications secondary to their small size. Additionally, this same population may require more frequent dialysis than older patients due to their dependence on fluids for nutrition and therefore benefit from a more readily recurring modality like PD. PD is also medically indicated in patients who cannot establish vascular access, receive anticoagulation, or safely tolerate rapid fluid removal. For the pediatric patient who lives far from a pediatric HD center and may not be large enough to dialyze at a local adult center, PD would be indicated to avoid the potential family disruption created by constant travel for regular HD treatments.

TABLE 75.1 Indications and Contraindications of Peritoneal Dialysis in Children

Indications
Infants and young children
Hemodynamic instability
Lack of vascular access sites
Contraindications to anticoagulation
Residing long distance from pediatric hemodialysis center
Contraindications (Absolute)
Abdominal wall defects, such as gastroschisis and omphalocele
Bladder exstrophy
Diaphragmatic Hernia
Unsuitable peritoneum due to extensive adhesions or malignancy
Peritoneal membrane failure
Contraindications (Relative)
Lack of adequate caregiver support
Pending abdominal surgery(-ies)
Presence of ileostomy or colostomy
Imminent (<3 months) kidney transplant
Caregiver or older patient preference

The only absolute contraindications to PD in children are conditions that compromise the abdominal cavity (congenital anomalies) or peritoneum (see Table 75.1). The relative contraindications to PD in children include scenarios that may compromise the peritoneum (abdominal surgery), the success of a home therapy (lack of caregiver capability or desire), or the need for long-term treatment (imminent transplant). Other medical conditions that affect the anterior abdominal wall, such as prune belly syndrome or the presence of an ostomy (gastrostomy, colostomy, vesicostomy, or ureterostomy), do not preclude consideration of PD. The increased risk of infection in patients with an ostomy may be mitigated by appropriate PD catheter placement and vigilant exit site care. Observational data suggest that PD may also be an acceptable modality in patients who have a ventriculoperitoneal (VP) shunt.

After evaluating the patient and caregivers for possible indications or contraindications to PD, any discussion about dialysis modalities should highlight the advantages and disadvantages of PD (see Table 75.2). There are no direct comparative studies of PD to HD in children to suggest superiority of one modality over the other, so the

TABLE 75.2 Advantages and Disadvantages of Peritoneal Dialysis in Children

Advantages
Preservation of residual renal function
Decreased all-cause mortality and cardiovascular risk
Lower rates of bacteremia and septicemia
Greater daytime patient and family independence (school attendance, parental work schedules)
Tailored prescription to individual patient and family lifestyle preferences
Fewer dietary and fluid restrictions
No need for vascular access and needle sticks
Disadvantages
Higher risk of infections and hospitalizations
Risk of hernia development (up to 40%)
Risk of caregiver burnout
Body image disturbances
Greater night-time restrictions

critical issue for families often becomes one of quality of life. However, there are some distinct differences in medical outcomes between the two modalities. Like in adults, residual renal function is better preserved in children receiving PD, which conveys certain benefits in terms of fluid and middle molecule clearance. Multiple studies have suggested better growth rates in children receiving PD compared to HD, whether from the preservation of residual function or other associated factors with this treatment. Also, similar to adult studies, pediatric PD recipients have lower all-cause mortality than HD patients, which is likely a product of renal function preservation. Cardiovascular morbidity, as measured by hospitalization rates for related complications, is also reduced in children on PD compared to HD.

The other distinct and often cited advantage of PD is the flexibility it affords as a home therapy option available to children. As there are options for automated treatments at night, it facilitates regular school attendance in children, while also allowing caregivers to work during the day. The greater frequency of treatment, nearly every day (or night), may permit less dietary restriction of fluid or phosphorus. However, these same advantages come at a potential price. The shift of the burden of responsibility to perform treatments from the in-center medical professional to the at-home provider can increase the potential stress on the caregivers and the home environment. Night-time treatments can be complicated by patient discomfort or machine alarms, keeping both the patient and caregiver awake and leading to physical fatigue. Additionally, the regimented nature of the modality lends itself to quickly leading to burnout. This, in turn, can lead to poor adherence to infection prevention measures or even performing treatments themselves. Thus, the demands of the modality on unprepared caregivers could be a source of potential patient compromise and negate one of the modality's perceived advantages.

One of the distinct disadvantages of PD is a higher overall rate of hospitalization and infections. This higher rate of infection has not been directly associated with provider burnout, as the rates of access-related infections are reportedly the same between PD and HD in the United States, but most pediatric dialysis providers can likely recount anecdotes of when a caregiver recalls deviation from their preventive regimen, subsequently leading to an infectious complication. Because of this potential risk of home provider burnout, a thoughtful evaluation of the patient and family's medical condition, social motivations, existing support system, and physical and economic capabilities by the multidisciplinary team of physicians, nurses, social workers, and other health professionals (psychologists, child life specialists) is warranted. An advanced assessment of the home environment should also be considered, if PD is being considered, to confirm the availability of electricity, water, telephone, and physical space to perform treatments safely. Discussions with the caregivers should also acknowledge that chronic PD is merely one form of treatment in the continuum of renal replacement therapies, not the quintessential therapy, as up to 20% of pediatric PD patients will need to change to HD at some point.

Prescription Components

The prescribing of PD historically has been performed empirically, with family lifestyle and dialysis center preferences often being the predominant determinants. However, with advances in the size and safety of equipment as well as improved automated technology, there are increased options available with PD so that it may be tailored to the individual patient's needs, such as age, size, and residual renal function, in addition to lifestyle. Thus, the PD prescription should take into account its clinical impact, including overall patient safety, in addition to its psychosocial impact.

The PD alternatives available in children are similar to those in adults, with both manual and automated options. Continuous ambulatory PD (CAPD) entails manual exchanges during the day, with a long dwell occurring overnight, to provide continuous solute removal. It has been prescribed to children throughout the world as it is less costly to perform, so it may be preferred for some patients for this reason. CAPD is generally more effective in children with residual renal function. With the advances in connection technology, there is now a reduced risk of infectious complications associated with accessing the PD catheter frequently during the day in CAPD. However, there are limited options to the volumes of PD solution bags, making CAPD difficult in smaller patients who will have more variable fill volumes. Also, the inconvenience of manual exchanges during the day makes it less desirable for some patients, which likely contributes to its low usage rate.

One North American dialysis registry recently reported that CAPD was used in 16%–21% of pediatric PD patients, although this percentage varied greatly by individual pediatric dialysis centers.

Automated PD, in which a cycler performs the exchanges, has been the preferred modality in children because it allows for a variety of treatment options while also minimizing the work of, and risk of error by, its operator. Modern cyclers have programming options that allow for very small (60 mL) volumes of exchange, low flow rates, concomitant use of different dialysates, and variation in drain volumes. There are three automated options utilized with most cyclers. Nightly intermittent PD (NIPD) entails automated exchanges at night without a last fill, so no effective dialysis during the day. This lack of a daytime exchange provides less clearance of middle-sized molecules but allows for normal intraperitoneal pressure during the day with less risk of hernias and feelings of fullness, which may be desirable in younger patients who have feeding difficulties. The addition of a last fill converts NIPD to continuous cycling PD (CCPD), which has greater clearance but also has more protracted exposure of the peritoneum to glucose and increased dialytic losses of amino acids and protein. Tidal PD is a variation of automated PD with incomplete emptying of the peritoneal cavity with each exchange. This can provide more continuous exposure to dialysate but is often utilized more to alleviate drain pain or abate any mechanical drainage issues rather than providing greater solute clearance.

There are some physiologic advantages of using automated PD in addition to its conveniences. As exchanges take place at night, while the patient is recumbent, there is the recruitment of a greater amount of functional peritoneal surface area, allowing for greater clearance for the volume of dialysate. Additionally, intraperitoneal pressure is lower when lying down than when upright, so there may be better tolerance of fill volumes and possibly less hernia risk.

The determining factors for the choice of dialysate solution, fill volumes, and dwell times in pediatric patients are similar to those in adults, with few exceptions. More biocompatible solutions are preferred, if available. Bicarbonate-based dialysate has been associated with less inflow pain and better correction of acidosis compared to lactate-based solutions in children on PD. Solutions with lower glucose concentration are preferred as long as adequate fluid removal is provided. Other osmotic agents, like amino acids and glucose polymers such as icodextrin, have been used in children, although icodextrin is not as effective with fluid removal in younger children compared to older children and adults.

Goal fill volumes in children should be based on the patient's body surface area. In children greater than 2 years of age, the recommended fill volume is 1000–1200 mL/m^2 per exchange, similar to adults. The upper limit of fill volume in children and adolescents may be up to 1400 mL/m^2 as this corresponds to an intraperitoneal pressure of 14 cm of H_2O, the upper limit of safe pressure in children. However, in children less than 2 years of age, the recommended fill volume is only 600–800 mL/m^2 per exchange, as the peritoneal membrane surface area is much greater per unit of weight in infants than in adults. As there is a much higher rate of hernias seen in children, up to 40%, a graduated increase in fill volumes up to the recommended range, while being mindful of this risk, may be conducive in children. The optimal dwell times for children are best determined by evaluating the peritoneal membrane's transport characteristics, such as by Peritoneal Equilibration Test (PET). As this evaluation may not be performed until a few months after the initiation of PD, its results will be unknown at the advent of PD but should be sought during the course of therapy. An initial empiric dwell time of 1 hour is often used in infants, while older children may tolerate shorter dwell times. A large cohort study of ultrafiltration volumes in pediatric PD patients found that it was directly influenced by the number of cycles and inversely associated with the dwell time; therefore, volume status may be optimized using these shorter dwell times.

One aspect of the PD prescription that often gets overlooked, and is essential to sustained use of the modality, is the training of the home providers. As PD is a quotidian regimen, it is recommended that a minimum of two caregivers should be trained how to properly perform PD, with expectations that the nonprimary provider(s) regularly place the patient on and off PD in order to maintain their skills while also minimizing the risk of burnout to the primary caregiver. Children who are the age of assent (11 years of age and older) and developmentally appropriate should participate in their own care and may also be instructed, but the ultimate responsibility of care rests with the adult caregivers. The goals of home PD training are to instruct the caregivers on how to perform the procedure safely and to recognize and treat the complications of PD. There should be overall objectives of the training, but the instruction itself should be tailored to the caregivers' learning needs. The duration of training will vary based on the learners, but it should allow for ample opportunities to practice and demonstrate the procedures being taught. Prolonged training, as done in some countries, is associated with improved outcomes such as lower infectious complications, so it may be advantageous if the patient's clinical condition would allow for it. The timing of the training can also be critical, but it is preferably done when the patient is not admitted to the hospital to minimize any potential distractions to the caregivers.

Prevalence of Peritoneal Dialysis Use in Children

Worldwide, PD continues to be the most popular dialysis modality in children. Previous estimates of prevalent use ranged from 50% to 70% of children receiving dialysis in North America and Europe, with even higher percentages presumed in developing countries, although accurate global demographic data have historically been lacking. Some of this presumption is based on the rapidly expanding number of dialysis patients in developing nations, most of which

are adults, with the growing proportion of these patients receiving PD. However, it is also based on the presumptive costs of dialysis therapy, as PD is considerably less expensive than HD, especially in younger children. Chronic PD therapy has been shown to be practiced successfully in children in several developing nations throughout the world, with seemingly greater acceptance of its use. The International Pediatric Peritoneal Dialysis Network (IPPN) registry now collects data from over 84 nations, representing over 80% of the world's pediatric population.

Despite several features that would make PD more ideally suited for the pediatric population, recent trends would suggest that it is being prescribed less in children and is no longer the dialysis modality of first choice in the United States. The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) registry has collected data on children receiving dialysis at children's hospitals across North America since 1992. Data from its most recent comprehensive report showed that the percentage of children receiving PD, compared to HD, in North America has been steadily declining, from 65.3% in 1992 to 55.7% in the years 2008 to 2010. Additionally, U.S. Renal Data System (USRDS) data has revealed HD to be the most common initial therapy for ESRD in children aged 0–19 years since 1994, while remaining more prevalent than PD in this population. Most recent USRDS reports cited that only 29.5% of pediatric patients initiated ESRD care with PD, compared to 54.4% initiating with HD. Similarly, Canadian Organ Replacement Registry (CORR) data have shown a steady decrease in the prevalent use of PD in their pediatric ESRD population since the 1990s, while HD prevalence has remained about the same. Most recent CORR data showed that PD was the initial dialysis therapy used in children aged 0–19 years only 38% of the time, almost consistently from the years 2005–14.

The discrepancy between NAPRTCS and USRDS prevalence data potentially reflects some of the differences between pediatric academic institutions and adult dialysis units, as it is estimated that 25% of all pediatric dialysis patients receive their care at nonpediatric centers. However, the most recent NAPRTCS benchmarking data, collected from only a select 25 of the participating centers in the registry, revealed that HD surpassed PD as the modality of choice at the initiation of dialysis starting in 2015, while PD patients comprised only 48% of the total number of prevalent dialysis patients. This data trend showing less prevalent PD among pediatric institutions is worrisome since there is less comfort with this modality's use or the potential of a changing demographic of pediatric ESRD patients. If it is the former, then perhaps greater education of patients, caregivers, and prescribers may ensure the most appropriate prescribing of this modality in this more ideally suited population. It is still hoped that a referral to a pediatric-based dialysis unit, with greater comfort and experience with this population both in terms of surgical placement of access and psychosocial aspects of ESRD, would increase the appropriate use of PD.

Recommended Reading

Borzych-Duzalka D, Schaefer F, Warady BA. Targeting optimal PD management in children: what have we learned from the IPPN Registry? *Pediatr Nephrol.* 2021;36:1053–1063.

This article discusses the challenges of data gathering of PD in children from a global perspective as well as summarizes the core findings from several studies performed from this international registry, including variation of practice outcomes based of national economic differences.

KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for 2006 updates: hemodialysis adequacy, peritoneal dialysis adequacy and vascular access. *Am J Kidney Dis.* 2006;48(suppl 1):S1–S322.

This monograph offers a series of evidence-based guidelines on criteria for the initiation of dialysis and selection of modality, with a specific section (Guideline 6) focusing on pediatric PD.

Watson AR, Gartland C. Guidelines by an ad hoc European Committee for Elective Chronic Peritoneal Dialysis in Pediatric Patients. *Perit Dial Int.* 2001;21:240–244.

This guideline gives recommendations on advanced family preparation for PD as well as essential elements of home training.

Warady BA, Schaefer F, Bagga A, et al. Prescribing peritoneal dialysis for high-quality care in children. *Perit Dial Int.* 2020;40(3):333–340.

These expert guidelines give recommendations regarding the initiation, modality selection, small solute clearance, and fluid removal for children receiving peritoneal dialysis, based off a review of current literature, including summaries on key studies in each area.

Verrina E, Cappelli V, Perfumo F. Selection of modalities, prescription, and technical issues in children on peritoneal dialysis. *Pediatr Nephrol.* 2009;24(8):1453–1464.

This review discusses dialysate solutions, modalities, and technical issues with pediatric PD.

United States Renal Data System. 2018 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. Volume 2: End-stage Renal Disease in the United States. Chapter 7: ESRD among Children, Adolescents. In: *and Young Adults.* Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases; 2018:463–500.

This annual report shows patterns of dialysis modality selection and their respective morbidity and mortality rates for pediatric ESRD patients in the United States.

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Nutritional Management of Children Undergoing Peritoneal Dialysis

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Nutritional management is a key component of the care of children treated with peritoneal dialysis (PD). This includes regular assessment of nutritional status as well as development and implementation of a dietary prescription. Optimal nutritional management requires collaboration among the child, the caregivers, a renal dietitian, and other members of the multidisciplinary pediatric nephrology team. The goals are to achieve normal growth, development, and body composition and to avoid the complications associated with malnutrition and electrolyte disturbances. Although growth failure is recognized as one of the distinctive features of children with chronic kidney disease (CKD), it is not inevitable. Adequate growth is achievable and is a good indication of adequate nutrition over the long term. Because height has an important impact on self-esteem and perceived quality of life, normal final adult height should be the goal for all children.

It is useful to consider both the patterns and drivers of growth in healthy children when approaching children treated to PD. The infancy phase of growth is dominated by nutrition, the childhood phase by growth hormone, and the pubertal phase by sex hormones. Children with CKD may have disturbances in all of these factors, including a delay in the transition from the infancy phase to the childhood phase (which results in a slower than normal growth velocity). In infancy, poor caloric intake caused by anorexia is the main contributor to growth impairment, but energy intakes for older children with CKD are usually normal relative to size. A much larger proportion of the daily energy requirement is devoted to growth in infants than in older children. Poor appetite may result from a combination of factors, including a thirst for water rather than food, administration of unpleasant medications, disordered gastric motility, and dysregulation of appetite-regulating cytokines and hormones.

It is important to note that not all abnormalities in growth and body composition in children treated with PD are related to inadequate nutrition. Other factors may also play a role in the wasting—or "cachexia"—that may occur in CKD, including systemic inflammation, endocrine perturbations, and abnormal neuropeptide signaling.

Assessment of Growth and Nutritional Status

Growth Parameters

As for healthy children, the recommended frequency for assessment of growth and nutritional status in CKD depends on the age of the child (Table 76.1) and should be individualized according to clinical status. On average, growth assessment should be done four times as often in children treated with PD compared with healthy children. Basic measurements include weight for age, stature for age (recumbent length in children younger than 24 months, standing height for those older), and head circumference (in children 3 years and younger). It is recommended that the World Health Organization (WHO) growth charts be used as a reference from birth to 2 years because these standards represent ideal growth (which should be the goal for children with CKD). After age 2 years, there is minimal difference between the U.S. Centers for Disease Control and Prevention (CDC) reference curves and WHO growth standards. Calculation of body mass index (BMI) is useful to see if the child's weight for height places them in an at-risk category (underweight, overweight, or obese). When plotting BMI relative to age in a child with growth or maturational delay, this may result in inappropriate underestimation of their BMI compared with peers of similar height and developmental age. This problem can be avoided by expressing BMI relative to height age rather than chronologic age in children with CKD. Height age is the age at which the child's height would be at the 50th percentile. Although the primary focus of nutritional assessment in children on PD has typically been to identify undernutrition, it is important to note that obesity is increasing in frequency.

Weight assessment can be challenging in children on PD because of changing volume status. "Dry weight" (i.e., euvolemic weight) should be estimated based on blood pressure, presence of edema, response to ultrafiltration, and serum albumin. The volume of the daytime dialysate dwell must be subtracted from the measured weight.

TABLE 76.1 Recommended Nutritional Assessment for Children with Stages 2 to 5D Chronic Kidney Disease

Measure	Minimum Frequency, by Age		
	0 to <1 Year	1–3 Years	>3 Years
Height or length for age percentile/SDS	Every 2 weeks to 1 month	Every 1 month	Every 1–3 months
Height or length velocity for age percentile/SDS	Every 2 weeks to 1 month	Every 1–2 months	Every 6 months
Estimated dry weight and weight for age percentile/SDS	Every 1 week to 1 month	Every 2 weeks to 1 month	Every 1–3 months
BMI for height age percentile/SDS	Every 2 weeks to 1 month	Every 1 month	Every 1–3 months
Head circumference for age percentile/SDS	Every 2 weeks to 1 month	Every 1–2 months	Every 1–3 months
Dietary intake	Every 2 weeks to 2 months	Every 1–3 months	Every 3–4 months

BMI, Body mass index; *SDS*, standard deviation score.

Dietary Intake

Information about dietary intake provides useful indices of nutrient quantity and quality. It is important to estimate total daily intake of calories, macronutrients (carbohydrate, protein, and fat), vitamins, and minerals. The most clinically feasible methods of determining usual dietary intake are the prospective 3-day dietary diary and the retrospective 24-hour recall (done three times, 1 weekend day + 2 weekdays). The retrospective 24-hour recall, although limited by its inability to capture the day-to-day variability in intake, may be more suitable for adolescents, in whom underreporting is common with 3-day dietary histories.

A skilled dietitian will also consider a number of other factors in a comprehensive dietary history, including any dietary or fluid restrictions and compliance with these restrictions, appetite changes affecting intake, feeding history, and relevant clinical information. *Feeding history* includes information on who is involved with preparation and offering of food (supervised or unsupervised child vs. primarily from caregivers), how the food is prepared and delivered (e.g., enteral feeding devices, oral), frequency and timing of feeds (daytime or nighttime), and any oral aversions, swallowing difficulties, reflux, or vomiting.

Other important clinical information includes urinary output, usual body weight (and trends), food security (capacity of family to afford feeds consistently), level of physical activity, and current dialysis prescription (may impact nutritional requirements based on glucose concentration of dialysis fluids and intake, e.g., early satiety because of daytime dwell volumes).

Physical Examination

A thorough physical examination is an important part of the nutritional assessment. The hydration status, presence or absence of edema, and blood pressure can provide useful guides as to the true dry weight. Signs of nutritional deficiency should be noted. The skin may be dry with excess flaking and uneven pigmentation, and the hair may be brittle, dry, and easily shed. Angular cheilosis and stomatitis, hepatomegaly, and certain neurologic abnormalities may each point to vitamin deficiencies. Genu deformities of the limbs, thickened wrists, costochondral beading (the rachitic rosary), and thickening of the wrists may point to vitamin D–deficient rickets.

Adequacy of Dialysis

It is important to remember that inadequate dialysis may result in poor appetite, nausea, deranged biochemical indices, hypertension, and edema. Dialysate clearances of urea normalized to total body water (Kt/V_{urea}) and the creatinine (CCr) normalized to body surface are measures of dialysis adequacy. Target Kt/V is at least 2.1 to 2.2 per week. Studies in children treated with hemodialysis (HD) showed that catch-up growth was achievable when higher than standard doses of HD were used (Kt/V > 2.0 per treatment). It is not known whether enhanced PD clearance would also result in better growth; achieving clearances much higher than recommended would be very difficult with PD because of limitations in feasible hours of treatment and fill volumes.

Dietary Prescription

The international Pediatric Renal Nutrition Task Force recently coined the novel term "Suggested Dietary Intake" (SDI). The SDI recognizes that different countries and organizations around the world recommend slightly different nutritional intakes for healthy children and that none of these is clearly superior to any other. Therefore, the SDI includes a range of values.

Energy

The lower and upper limits of the SDI for energy represent the lowest and highest published values (from different sources)

TABLE 76.2 Energy and Protein Requirements for Infants, Children, and Adolescents with CKD 2–5D Aged 0–18 Years

SDI for Energy and Protein, Birth* to 18 years

Month	SDI† Energy (kcal/kg/day)	SDI Protein (g/kg/day)	SDI Protein (g/day)
0	93–107	1.52–2.5	8–12
1	93–120	1.52–1.8	8–12
2	93–120	1.4–1.52	8–12
3	82–98	1.4–1.52	8–12
4	82–98	1.3–1.52	9–13
5	72–82	1.3–1.52	9–13
6–9	72–82	1.1–1.3	9–14
10–11	72–82	1.1–1.3	9–15
12	72–120	0.9–1.14	11–14

Year	SDI† Energy (kcal/kg/day)		SDI Protein (g/kg/day)	SDI Protein (g/day)
—	*Male*	*Female*		
2	81–95	79–92	0.9–1.05	11–15
3	80–82	76–77	0.9–1.05	13–15
4–6	67–93	64–90	0.85–0.95	16–22
7–8	60–77	56–75	0.9–0.95	19–28
9–10	55–69	49–63	0.9–0.95	26–40
11–12	48–63	43–57	0.9–0.95	34–42
13–14	44–63	39–50	0.8–0.9	34–50
15–17	40–55	36–46	0.8–0.9	Male: 52–65 Female: 45–49

*37/40 weeks' gestation. Premature infants have higher energy and protein requirements.
† SDI is based on the Physical Activity Level (PAL) used by the international bodies: 1–3 year PAL 1.4; 4–9 year PAL 1.6; and 10–17 year PAL 1.8. Where guidelines have given a range of energy requirements for different levels of PAL, the lowest PAL has been taken for SDI energy in consideration that children with CKD are likely to have low activity levels.
For children with poor growth, reference to the SDI for height age may be appropriate. Height age is the age that corresponds to an individual's height when plotted on the 50th centile on a growth chart. *CKD*, Chronic kidney disease; *SDI*, suggested dietary intake.
Reprinted from Shaw V, Polderman N, Renken-Terhaerdt J, et al. Energy and protein requirements for children with CKD stages 2–5 and on dialysis—clinical practice recommendations from the Pediatric Renal Nutrition Taskforce. *Pediatr Nephrol*. 2020;35(3):519-531. Licensed under a Creative Commons Attribution 4.0 International License. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

for the daily amount of energy considered sufficient to meet the needs of half the population. The range of SDI values suggested for children with CKD assume the lowest level of physical activity. Energy requirements for children treated with PD should be considered to be 100% of the SDI for healthy children of the same chronologic age (Table 76.2). Children younger than 3 years old with a length- or height-for-age standard deviation score (SDS) below −1.88 and failing to achieve expected weight gain and growth when receiving SDI for chronologic age should be prescribed an energy intake relative to height age. Energy prescriptions should be tailored based on the child's weight and height gain; the calorie contribution from PD fluid must also be taken into consideration.

A balance of calories from carbohydrate and unsaturated fats within the physiologic recommended ranges is suggested (Table 76.3).

Protein

The lower and upper limits of the SDI for protein represent the lowest and highest published values (from different sources) for the daily amount of protein considered sufficient to meet the needs of nearly all (97.5%) of the population). Protein requirements vary with age and sex and may be higher during recovery from an acute illness (e.g., peritonitis). It is currently recommended that children on PD receive a protein intake at the upper end of the SDI (see

TABLE 76.3 Accepted Macronutrient Distribution Ranges

Macronutrient	Children 1–3 Years	Children 4–18 Years
Carbohydrate	45%–65%	45%–65%
Fat	30%–40%	25%–35%
Protein	5%–20%	10%–30%

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Table 76.2). The recommendation from the 2008 Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines suggested that children on PD receive 100% of the dietary reference intake (DRI) (which would meet the needs of 97.5% of the population) for protein, plus an additional 0.15 to 0.3 g/kg/day to account for protein losses in the dialysate. Peritoneal permeability for protein shows large interpatient variability but can be assessed in each patient by calculating daily PD protein losses. Peritoneal protein losses decrease with age from an average of 0.28 g/kg in the first year of life to less than 0.1 g/kg in adolescents. Using the SDI may simplify the estimation of protein needs. The lower limit of the SDI is considered the minimum safe protein intake. Low-protein diets are not recommended in children based on the results of a randomized trial showing compromised growth in infants receiving low protein diets. The use of protein supplements to augment inadequate oral intake should be considered in children on PD who are unable to meet requirements through their regular diet alone.

Children consuming a vegetarian or vegan diet require additional protein due to the lower bioavailability of plant-based protein compared with animal protein. The suggested protein intake for lacto-ovo vegetarians is 1.2 times higher than for those taking a mixed plant- and animal-based diet and 1.3 times higher for vegans. It is also important to recognize that many meat-based protein sources contain significant amounts of phosphate, which should be included in the daily phosphate intake.

Dietary protein intake can be estimated either by diet history or by determination of the protein equivalent of nitrogen appearance (PNA), calculated by measuring the urea nitrogen content of urine and dialysate and multiplying by a constant (6.25 − the number of grams of protein per 1 g of nitrogen). In children, body size-adjusted formulas to estimate PNA have been developed but are not in common use. There are concerns about their validity in highly anabolic or catabolic states. However, theoretically, PNA should provide an objective estimate of protein intake.

Lipids

Dietary lipids are the main energy source in a typical infant diet, contributing about 35% of the energy required and about 90% of the energy retained during the first 6 months of life. Lipids play crucial roles in central nervous system development as well as autocrine and paracrine signaling. Additionally, fats may increase the appeal of food by enhancing taste, texture, and aroma.

In children and adolescents on PD therapy, reported rates of dyslipidemia vary from 29% to 87%. Given the high risk of cardiovascular disease (CVD) in children with CKD, nutritional counseling should suggest the use of sources of unsaturated fat rather than saturated or trans fats and, when possible, to choose complex carbohydrates over simple sugars. Both primary and secondary prevention studies provide strong evidence that the consumption of fish and fish oils rich in EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) reduces CVD morbidity in adults. There are, however, safety concerns, including prolonged bleeding times, difficult glycemic control in patients with diabetes, and environmental contaminants in fish oil products. At this time, there is inadequate evidence to recommend routine use of omega-3 fatty acids to treat hypertriglyceridemia in children with CKD.

Fiber

Dietary fiber is found in most vegetables, fruits, and whole grains, which may be restricted in low-potassium and -phosphorus diets. Meeting dietary fiber recommendations may thus be more difficult in patients with CKD when intake of these foods is limited. Constipation may lead to technical problems with PD; therefore, when dietary intake does not suffice, fiber should be added via the various mineral and electrolyte-free powdered forms of fiber available (e.g., Benefiber).

Calcium and Phosphorus

All children being treated with PD have abnormalities in calcium and phosphorus metabolism, putting them at high risk for metabolic bone disease and fractures. In CKD, multiple factors contribute to impaired calcium homeostasis. These include decreased intestinal absorption of calcium as endogenous production of calcitriol (1,25-dihydroxyvitamin D) declines, decreased spontaneous calcium intake, and decreased vitamin D receptor expression. Renal phosphorus clearance is greatly reduced, resulting in elevated blood phosphate levels, decreased calcium levels, and stimulation of parathyroid hormone (PTH) via direct and indirect mechanisms.

Careful attention to calcium and phosphorus intake is necessary to avoid complications, including metabolic bone disease and vascular calcification. Normal skeletal development depends on adequate calcium intake. Serum calcium levels should be maintained within the normal range. Intestinal calcium absorption may be boosted by increasing calcium intake (diet or tube feeds and calcium-containing phosphate binders) and by supplementation with α-calcidiol or calcitriol. Calcium salts prescribed as supplements should be taken between meals and separately from iron supplementation to improve absorption and achieve maximum effects.

Although negative calcium balance is initially the main concern in children on PD, excess calcium intake may result in vascular and other soft tissue calcification. Therefore, estimation of total calcium intake is necessary. The calcium content of dialysis fluids and calcium-based phosphate binders will both affect calcium load. It is recommended that the total calcium intake from all sources (including phosphate binders) should generally be within the SDI (Table 76.4). If a higher total calcium intake is needed to maintain normal calcium and phosphate levels, it is suggested that the calcium intake not exceed twice the SDI. The lower and upper limits of the SDI for calcium represent the lowest and highest published values reflecting the intake considered adequate for 97.5% of the population.

The recommended intake of phosphate for patients on PD with persistently elevated PTH or serum phosphate concentration is the lower limit of the SDI (see Table 76.4), which represents the lowest published values reflecting the phosphate intake considered adequate for 97.5% of the population. Serum phosphate levels should be maintained within the normal range for age. While hyperphosphatemia is most common, hypophosphatemia may occur under certain conditions, necessitating phosphate supplementation to avoid rickets.

It is important to recognize the potentially large contribution of phosphate additives to the total phosphate intake. A variety of phosphates are added to processed foods as preservatives and stabilizers. It is difficult to quantify the amount of phosphate present in foods as additives since these are not usually included in food labeling, but it may be substantial. Therefore, efforts should be made to identify sources of added phosphates in the diet and reduce these first. Other foods rich in phosphate, including dairy products, animal proteins, and whole grains, contain many beneficial nutrients that processed foods (containing added phosphates) do not.

Trends in serum phosphate levels should be evaluated in conjunction with trends in serum calcium and PTH levels. In children on PD, the target range for PTH is two to nine times that of healthy children. It may also be useful to measure serum 25-hydroxyvitamin D levels annually. If the serum level is below 30 ng/mL (75 nmol/L), the child should be supplemented with ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3).

TABLE 76.4 Summary of SDI (Suggested Dietary Intake) for Calcium and Phosphate in Children with Stages 2 to 5D Chronic Kidney Disease

Age	SDI Calcium (mg)	SDI Phosphate (mg)
0–<4 months	220	120
4–<12 months	330–540	275–420
1–3 years	450–700	250–500
4–10 years	700–1000	440–800
11–17 years	900–1300	640–1250

For children with poor growth, reference to the SDI for height age may be appropriate. This is the age that corresponds to their height when plotted at the 50th centile on a growth chart.

Reprinted from McAlister L, Pugh P, Greenbaum L, et al. The dietary management of calcium and phosphate in children with CKD stages 2–5 and on dialysis—clinical practice recommendation from the Pediatric Renal Nutrition Taskforce. *Pediatr Nephrol*. 2020;35(3):501-518. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

Micronutrients: Vitamins and Trace Elements

Micronutrients are essential components of a balanced diet and contribute to adequate growth and development in children. Children with CKD are at risk of micronutrient deficiencies because of inadequate intake, poor gastrointestinal absorption, and abnormal renal metabolism. Those on PD are at increased risk of deficiency from dialysis-related losses. Target intake for micronutrients is, in general, 100% of the DRI. The KDOQI guidelines (2008) recommend the administration of a water-soluble vitamin supplement.

Children with CKD may also be at risk for micronutrient excess due to reduced renal clearance. Vitamin A and vitamin B_{12}, in particular, were noted to be elevated in 81% and 77% of 112 children with CKD stages 3–5 (predialysis).

Fluids and Electrolytes

Fluid and electrolyte requirements vary based on primary kidney disease, residual kidney function, and renal replacement therapy modality.

Fluid

On average, 80% of an individual's total water intake is derived from drinking water, and the other 20% is from food. Children with oliguria or anuria should limit their daily fluid intake to avoid complications of volume overload (most notably hypertension). Attempts at fluid restriction may be futile if salt (± sugar) intake is not simultaneously restricted. High sodium intake will lead to increased extracellular fluid (ECF) osmolality, which will then stimulate thirst.

$$\text{Daily fluid restriction} = \text{Insensible fluid losses} + \text{Urine output} - \text{Amount to be deficited}$$

(This calculation should also take into account a reasonably expected amount of daily weight gain.)

Sodium

Children with polyuria (usually secondary to obstructive uropathy and renal dysplasia) will have polydipsia. In some cases, polyuria is due to renal salt-wasting. Sodium wasting results in volume depletion and impaired growth (as sodium supports normal expansion of the ECF volume needed for

muscle development and mineralization of bone). Infants on PD may also experience substantial sodium losses via dialysate, even when anuric, because of the large peritoneal membrane surface area for body weight. Negative sodium balance and resulting volume depletion may be substantial in infants on PD; severe hypotension with resulting neurologic deficits have been reported. Infants on PD should have sodium balance calculated and sodium supplementation considered.

Children on PD with hypertension (systolic or diastolic pressure ≥95th percentile) or elevated blood pressure (systolic or diastolic blood pressure ≥90th percentile and <95th percentile) may require sodium restriction as part of a comprehensive strategy for volume and blood pressure control. Restriction of sodium is usually within the range of 1 to 2 mmol/kg/day but should be individualized. Measures to decrease salt intake are listed in Box 76.1.

Potassium

Both hyper- and hypokalemia cause alterations in skeletal, myocardial, and smooth muscle contractility and cardiac arrhythmias may result. Therefore, control of potassium levels is important. The vast majority of potassium excretion occurs via urinary losses; only about 10% occurs through intestinal losses. When renal clearance of potassium drops, serum potassium levels rise. The risk of hyperkalemia can also be increased by acidosis, medications (angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, potassium-sparing diuretics), hemolysis (blood transfusions and tumor lysis), and urinary obstruction. Limiting dietary potassium is the primary way to maintain acceptable potassium levels. Potassium intake can also be reduced using potassium-binding agents such as sodium polystyrene or patiromer, which may be added to formula to remove potassium before feeding.

Some children on continuous PD may actually develop hypokalemia. For this subgroup, potassium may need to be supplemented orally or via addition to dialysis fluids.

Carnitine

L-carnitine has an important role in the regulation of fatty acid metabolism and adenosine triphosphate (ATP) formation in various organs. It is a biologically active amino acid derivative that may be deficient in children on HD, and some data support L-carnitine supplementation in this population. Far less information exists on the relationship between PD and carnitine deficiency. There is insufficient evidence to conclude that carnitine supplementation is required in the PD population; further studies are needed.

• BOX 76.1 Methods to Decrease Salt Intake

- Consuming fresh instead of canned or processed foods
- Reducing or eliminating salt added to foods at the table
- Substituting fresh herbs and spices for salt when cooking
- Decreasing fast food intake
- Avoiding, when possible, medications with high sodium content (e.g., antacids, laxatives, nonsteroidal anti-inflammatory drugs, sodium polystyrene sulfonate)

Delivery of Nutrition

Supplemental nutritional support, preferably by the oral route, should be given to children on PD whose usual energy intake fails to meet requirements resulting in suboptimal growth or weight gain for age. If oral supplementation fails, nasogastric or gastrostomy tube feeding should be considered. The schedule of tube feeding (top-up boluses versus overnight continuous gavage) and the formula will depend on age, significant gastroesophageal reflux, and nutrient requirements. The majority of infants on PD will require tube feeding. In the relatively rare situation in which an older child requires tube feeding, it may be beneficial to have the majority of tube feeds overnight to encourage daytime hunger and oral intake and allow for normalization of daytime activities. Gastrostomy tube feeding has some advantages over nasogastric tube feeding, such as the decreased risk of gastroesophageal reflux and maxillary and nasal inflammation, less social stigma (because the gastrostomy is not visible), and avoidance of negative oral stimulation. In addition, gastrostomy tube feeding may be associated with enhanced growth compared with nasogastric tube feeding, although this is uncertain. There is no evidence of increased bacterial or fungal peritonitis in children with established gastrostomy tubes (ideally placed before PD catheter placement).

Use of Recombinant Human Growth Hormone Therapy

The growth hormone-insulin-like growth factor 1 (IGF-1) axis is an important regulator of growth and metabolism. Abnormalities in this axis resulting in growth hormone resistance have been noted in children with CKD. These abnormalities include decreased expression of the growth hormone receptor, impaired signal transduction of the growth hormone receptor, decreased production of IGF-1, and decreased activity of IGF by inhibitory IGF-binding proteins. Clinical studies support the efficacy of recombinant human growth hormone therapy in patients on PD—earlier treatment results in a better response. Recombinant human growth hormone therapy should be considered if growth failure (height velocity for age SDS <−1.88 or height velocity for age <third percentile) persists beyond 3 months despite treatment of nutritional deficiencies and metabolic abnormalities. Linear growth targets should take into account the genetic predisposition via midparental height calculations.

Summary

The nutritional assessment of children on PD is a complex process that must be individualized. Frequent monitoring and dietary modifications may be necessary. With a team approach including a dietitian, nephrologist, renal nurses, parents or other caregivers, and patients, normal growth can be achieved.

Recommended Reading

Shaw V, Polderman N, Renken-Terhaerdt J, et al. Energy and protein requirements for children with CKD stages 2–5 and on dialysis—clinical practice recommendations from the Pediatric Renal Nutrition Taskforce. *Pediatr Nephrol.* 2020;35(3):519–531.

This provides an updated comprehensive evidence-based guidance to providing adequate energy and protein to children with CKD 2–5.

McAlister L, Pugh P, Greenbaum L, et al. The dietary management of calcium and phosphate in children with CKD stages 2–5 and on dialysis—clinical practice recommendation from the Pediatric Renal Nutrition Taskforce. *Pediatr Nephrol.* 2020;35(3):501–518.

This provides updated comprehensive evidence-based guidance to managing calcium and phosphate in children with CKD 2–5.

Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. Kidney Disease: Improving Global Outcomes (KDIGO) 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease—mineral and bone disorder (CKD-MBD). *Kidney Int Suppl.* 2017;7(1):1–59.

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Falkenhein M, Hartman J, Hebert L. Nutritional management of water, sodium, potassium, chloride, and magnesium in renal disease and renal failure. In: Kopple JD, Massry SG, eds. *Nutritional Management of Renal Disease.* 1st ed. Baltimore, MD: Williams & Wilkins; 1997:371–394.

This chapter describes fluid- and electrolyte-specific management in patients with CKD.

Foster BJ, Borzych D. Tube feeding in children with chronic renal insufficiency. In: Warady BA, Schaefer F, Alexander S, eds. *Peritoneal Dialysis.* Springer; 2011.

This chapter reviews the rationale underlying the use of tube feeding, the existing evidence supporting the use of tube feeding in children with renal insufficiency, and the indications for tube feeding.

Foster BJ, McCaulay L, Mak RH. Nutrition in infants and very young children with chronic kidney disease. *Pediatr Nephrol.* 2012;27(9):1427–1439.

Considers the mechanisms and manifestations of inadequate nutritional status in very young children with CKD, appropriate nutritional assessment techniques, and the approach to nutritional management of this special population.

Haffner D, Schaefer F, Nissel R, et al. Effect of growth hormone treatment on the adult height of children with chronic renal failure. German Study Group for Growth Hormone Treatment in Chronic Renal Failure. *N Engl J Med.* 2000;343(13):923–930.

This landmark study showed that persistent catch-up growth with recombinant human growth hormone therapy, leading to a majority achieving normal final adult height.

Karlberg J, Schaefer F, Hennicke M, et al. Early age-dependent growth impairment in chronic renal failure. European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood. *Pediatr Nephrol.* 1996;10(3):283–287.

This study describes the infancy, childhood, and pubertal phases of growth and how they are disturbed in childhood CKD.

Khan AN, Bernardini J, Johnston JR, Piraino B. Hypokalemia in peritoneal dialysis patients. *Perit Dial Int.* 1996;16(6):652.

This study describes hypo- instead of hyperkalemia in a significant number of patients on continuous peritoneal dialysis.

Mak R, Cheung WW, Zhan JY, Shen Q, Foster BJ. Cachexia and protein energy wasting in children with chronic kidney disease. *Pediatr Nephrol.* 2012;27(2):173–181.

Reviews the diagnostic criteria for and manifestations of cachexia and protein energy wasting (PEW) in CKD and considers the limitations and applicability of these criteria to children with CKD.

National Kidney Foundation. KDOQI clinical practice guideline for nutrition in children with CKD: 2008 update. *Am J Kidney Dis.* 2009;53(suppl 2):S1–S124.

This provides a comprehensive evidence-based approach to nutritional management in children with CKD, giving specific guidance on all aspects of nutritional management with detailed rationales.

Parekh RS, Flynn JT, Smoyer WE, et al. Improved growth in young children with severe chronic renal insufficiency who use specified nutritional therapy. *J Am Soc Nephrol.* 2001;12(11):2418–2426.

This study demonstrates that nutritional support with sodium and water supplementation can maintain or improve the growth of children with polyuric, salt-wasting CKD and suggests optimal fluid and sodium intakes for children with salt wasting.

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This study suggests that adequate nutrition in combination with enhanced dialytic clearance can promote normal growth and even catch-up in children treated with long-term hemodialysis.

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Peritoneal Dialysis in Neonates and Infants

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Introduction

Peritoneal dialysis (PD) has long been considered an effective treatment modality for neonates and infants with severe acute kidney injury (AKI) and is the dialysis modality of choice for patients in this age group with end-stage kidney disease (ESKD). Its popularity and success largely derive from its simplicity and effectiveness as a means of removing solute and fluid in even the smallest patients and because it is a well-tolerated procedure by most patients.

Peritoneal Dialysis as a Renal Replacement Modality for Acute Kidney Injury

There is limited literature documenting the etiology of AKI that results in the need for acute PD in this population. However, some generalizations can be made. In most cases, congenital malformations such as renal dysplasia or posterior urethral valves do not compromise kidney function so severely that dialysis is required in the newborn period. Instead, acquired renal disorders, usually related to perinatal asphyxia, hypoxia, sepsis, hypovolemia, and cardiac surgery, make up the majority of insults that mandate acute replacement therapy. Very rarely, acute vascular events such as renal artery or renal vein thrombosis are to blame, but these insults usually have to affect both kidneys to result in AKI requiring dialysis.

Despite the growing popularity of continuous renal replacement therapy (CRRT), survey results of pediatric nephrologists provide evidence that PD remains the predominant acute dialysis modality for children <2 years of age. Access can be placed emergently at the bedside in patients who are too unstable to undergo a surgical procedure. Additionally, PD can typically be performed safely and effectively in patients with cardiovascular instability as a result of the inherent gradual and continuous provision of both ultrafiltration and solute clearance characteristics of the procedure. Recently, several studies have demonstrated improved outcomes associated with prophylactic placement of a PD catheter and early initiation of PD in infants undergoing cardiac surgery. One randomized prospective trial comparing PD versus furosemide in this population showed improved fluid management, less inotrope use, and a shorter duration of mechanical ventilation in the PD group. Finally, PD offers the additional advantage of not requiring systemic anticoagulation, in contrast to hemodialysis (HD) and CRRT.

There are rare absolute contradictions to PD in neonates, such as omphalocele, diaphragmatic hernia, or gastroschisis, all scenarios in which there is essentially the lack of a functional peritoneal cavity. Relative contraindications to PD include the presence of severe pulmonary disease since the increased intra-abdominal pressure associated with PD could further compromise pulmonary function, or a history of extensive abdominal surgery because of the possible presence of adhesions and a compromised peritoneal cavity. The presence of a vesicostomy or colostomy or the diagnosis of polycystic kidney disease is not a contraindication to PD, although the risk of peritonitis may be greater in this setting. With these issues in mind and given the lack of prospective trials comparing the outcomes of neonates and infants with AKI stratified by dialysis modality, the decision regarding dialysis modality selection always needs to factor in local resources and expertise along with the patient's clinical status.

Peritoneal Dialysis Access in Acute Kidney Injury

The two most commonly placed accesses for acute PD are the percutaneously placed Cook catheter and the surgically placed Tenckhoff catheter. The Cook catheter offers the advantage of bedside placement by a nephrologist or intensivist via the Seldinger technique. Since only local anesthesia is required, it can be placed promptly, even in an unstable patient. However, its use has been associated with a high rate of complications such as leakage of dialysis fluid from the catheter entry site on the abdominal wall and catheter obstruction. Chadha et al., in a single-center retrospective study of infants and young children with AKI, found that

by day 6 of dialysis, only 46% of Cook catheters were functioning without complications. In comparison, they found that over 90% of surgically placed Tenckhoff catheters were free of complications at the same time point. Thus the authors suggested that if acute dialysis is expected to be required for more than 5 days, a Tenckhoff catheter should either be placed initially, or elective replacement of the Cook catheter with a Tenckhoff catheter can be performed in a timely manner. Subsequently, the same center reported promising results with the use of a multipurpose percutaneous catheter (Cook Mac-Loc Multipurpose Drainage catheter) in a small cohort of infants with AKI who experienced a mean complication-free catheter survival of approximately 11 days. Finally, another recent small series described the successful use of a 16 G single-lumen central venous catheter placed as a PD catheter via the Seldinger technique in 5 infants with severe AKI after cardiac surgery.

The most important consideration for the successful placement and function of a Tenckhoff catheter in this population is the experience of the surgeon. This can be particularly problematic at centers caring for a small number of patients overall, where the need to provide dialysis to a very young infant may be a rare event. Because of the importance of the access and the desire for the outcome of placement to be complication free, the surgical placement should ideally be limited to only a few surgeons per center; on rare occasions, it may be preferable to refer the patient to another, more experienced center for access placement, in a manner similar to what has been recommended for vascular access.

Prescription Considerations for Acute Kidney Injury

In the acute setting, the prescription of PD is guided by the need for low dialysate fill volumes to prevent dialysate leakage and keep the intraperitoneal pressures (IPPs) as low as possible to avoid any respiratory embarrassment. Typically, initial dialysis fill volumes for neonates/infants should be approximately 10 mL/kg body weight (300 mL/m^2) and are gradually increased as clinically warranted and tolerated up to a maximum volume of 30–40 mg/kg. Because these initial low volumes result in a rapidly diminished dialysate osmotic gradient and resultant limited ultrafiltration, dwell times of 1 hour or less are frequently utilized. Dwell times as short as 20 minutes have also been used in neonates when rapid removal of small solutes is desired. Despite the inefficiency introduced by using low dialysate volumes, adequate solute clearance and ultrafiltration rates can be achieved if exchanges are performed around the clock. Golej et al. reported a case series of 116 neonatal and pediatric patients who underwent low-volume PD in whom the mean ultrafiltration rate was 2.8 mL/kg/h. A negative fluid balance was accomplished in 53% of patients, despite the presence of hemodynamic instability in a majority of the subjects. Several patients who presented with hyperkalemia and metabolic acidosis did require the use of higher fill volumes to control the biochemical abnormalities adequately.

In extreme cases of hyperphosphatemia or hyperammonemia, continuous-flow PD (CFPD) has been employed. CFPD requires the placement of two intraperitoneal catheters, with one catheter used for influx and another for efflux of dialysate. In this manner, the transport potential of the peritoneal membrane is maximized by maintaining the highest possible solute concentration gradient. Dialysate flow rates of up to 300 mL/h in patients as small as 3 kg have been described using this technique.

The lower dialysate fill volume employed in the neonate generally necessitates the use of manual exchanges early in the course of PD, in contrast to an automated cycling device. Advantages of manual exchanges include the low expense and technical simplicity. Neonatal or pediatric intensive care unit (PICU) nurses can be trained to perform manual exchanges, which avoids the need for a dialysis nurse to continuously supervise therapy. Indeed, the combination of simplicity, low cost, and efficacy makes PD with the use of manual exchanges in the neonatal setting an attractive option for centers with limited resources. There are several commercially available manual exchange sets (Baxter, USA; Fresenius, USA; Gesco International, USA; Medionics International, CA; and Utah Medical Products, USA) that minimize the risk of contamination and allow for the warming of dialysate before it is instilled into the patient.

In contrast to manual exchanges, there are automated cyclers that permit the accurate delivery of a fill volume as low as 60 mL, with low-flow drainage modes to avoid unnecessary alarms (Home Choice Pro, Baxter). Practically, automated PD (APD) can be performed using the cycling device without a substantial recirculation volume in the dialysis tubing when the fill volume is more than 100 mL. The volume of tubing to the patient using a "low volume" set is approximately 19 mL.

Standard commercially available dialysis solutions are employed in the acute setting with the choice of dextrose concentration (1.5%, 2.5%, or 4.25%) driven by the need for ultrafiltration. The choice of PD solutions is also largely dependent upon their availability in different regions of the world. In the United States, only lactate-buffered solutions are available, whereas bicarbonate-buffered solutions, which are presumably more biocompatible, are available in Europe and other geographic regions. Ideally, when bicarbonate-buffered solutions are available, lactate-based solutions should be avoided in neonates/infants with severe acidemia as lactate needs to be converted by the liver to the effective base.

The Chronic Setting: End-Stage Kidney Disease

Peritoneal Dialysis as a Renal Replacement Modality for End-Stage Kidney Disease

Many of the same considerations that favor PD as a renal replacement modality for AKI apply in the setting where long-term dialysis is needed. The high rates of both infectious and mechanical complications of HD when provided to the youngest infants makes its use over long periods of

time impractical in most situations. For patients receiving HD for extended periods of time, access revision rates for young infants are estimated at 40%. Couple these issues with the recognition that long-term HD access in a neonate or infant consists of a central venous catheter, a practice that is accompanied by the significant potential for infection, stenosis of central veins, and the resultant inability to create a fistula in the future for patients who face a lifetime of ESKD care, and one can fully understand the preferential selection of PD as the chronic dialysis modality of choice for neonates and infants.

Chronic PD is particularly advantageous compared to HD for the neonatal/infant patient for reasons other than access. Meeting the nutritional needs of neonates can be challenging, especially with the severely oliguric/anuric patient who must receive formula volumes as high as 150 mL/kg of body weight per day. The relative ease with which the fluid status can be managed with PD on a daily basis precludes the fluctuations of body volume and, potentially, blood pressure inherent to intermittent HD. Multiple studies have also suggested that better growth rates can be achieved in patients on PD compared to HD. Recent data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) show improvements in height standard deviation score (SDS) scores at 24-month follow-up of patients who initiated PD at less than 1 year of age, while SDS scores remained unchanged for those on HD. Finally, PD promotes gradual expansion of the abdominal cavity in preparation for successful renal transplantation. This takes on added importance when one considers that the parents of these young children often serve as living donors and mandate the need to insert an adult-sized kidney into a recipient who may have a bodyweight of only 10 kg.

Peritoneal Dialysis Access for End-Stage Kidney Disease

Long-term PD mandates the surgical placement of a Tenckhoff catheter. As in the setting of AKI, the most important consideration for its successful placement and function in the neonate and infant with ESKD is the experience of the surgeon. If complications such as dialysate leakage are to be avoided, placement of the catheter 2–3 weeks before its eventual use is ideal so that there is an opportunity for ingrowth of the Dacron cuffs of the catheter into surrounding tissues. The provision of fibrin sealant at the peritoneum as a means of achieving a tight closure when a delay in PD initiation is not possible has been practiced. Additional considerations in the chronic setting are the orientation of the subcutaneous tunnel of the catheter, the exit-site orientation and location, the potential need for an omemtectomy, and timing of placement with respect to concurrent or future placement of a gastrostomy tube (G-tube).

Observational data from the NAPRTCS, which are reflected in the International Society for Peritoneal Dialysis (ISPD) peritonitis guidelines, suggest that Tenckhoff catheters with a downward pointed exit site are associated with the lowest peritonitis rates, a characteristic (along with the possible preference for two cuffs) that should be considered for all chronic PD catheters placed in neonates and infants because of the increased rates of peritonitis they experience compared to older children. The catheter exit site should also be placed outside of the diaper area and away from any potential ostomy site (e.g., on the right side of the abdomen for any patient in whom G-tube insertion is possible) with the superficial cuff located approximately 2–3 cm from the skin surface. Occasionally, this necessitates placement of the exit site on the chest wall. Given the small size of the neonatal/infant patient, these requirements can be difficult to accommodate and, as noted earlier, require a very skilled and experienced surgeon.

As suggested previously, one additional unique consideration in this age group is the timing and location of PD catheter placement relative to G-tube placement in order to accommodate nutritional requirements (see later). The catheter exit site should ideally be placed at a distance (often the contralateral side) from the site of a current or potential gastrostomy to decrease the risk of contamination and possible peritonitis. Likewise, it is recommended that, when possible, the PD catheter be placed either simultaneously with or after placement of a G-tube to avoid contamination of the peritoneum with gastric contents and the possible development of peritonitis. When the PD catheter placement precedes G-tube placement, the latter procedure should take place under prophylactic antibiotic and antifungal therapy. A recent retrospective study of 13 pediatric PD patients who underwent G-tube placement after PD catheter placement demonstrated a similar safety profile between laparoscopic gastrostomy and open G-tube placement.

Prescription Considerations in End-Stage Kidney Disease

Historically, the prescription of PD in infants was based on the perception that the pediatric peritoneal membrane, especially in infants, had different solute transport properties than that of an adult. This was in large part based on the results of early studies in which dialysis fill volumes were based on body weight. When scaled to body weight, the surface area of the infant peritoneal membrane is almost twice that of a 70-kg adult. Thus, the use of weight-based volumes results in a relatively low fill volume, which in turn results in more rapid solute equilibrium and the inaccurate perception of an inherent increased solute transport capacity. In contrast, the provision of a fill volume in young children scaled to body surface area (BSA) takes into consideration the age-independent relationship of BSA to peritoneal surface area and makes possible the accurate assessment of membrane transport capacity during the performance of a Peritoneal Equilibration Test (PET). Indeed, when Warady et al. based fill volumes on BSA, peritoneal membrane transport capacity in children was similar across the pediatric age range and to adults.

Whereas it is important to prescribe the fill volume scaled to BSA to optimize solute equilibration and ultrafiltration, it is equally important not to provide too large

a fill volume that may lead to an excessive increase in IPP (>18 cm H_2O). The latter development can result in reduced dialysis efficiency due to enhanced lymphatic uptake from the peritoneal cavity, in addition to poor tolerance by the patient. Accordingly, the recommended maintenance fill volume for patients below age 2 years is limited by patient tolerance and is generally 600–800 mL/m^2. This is in contrast to a volume of approximately 1100–1200 mL/m^2 that is recommended for older children and adolescents. As mentioned earlier, a smaller, manually delivered volume is typically used when the neonate is started on dialysis and is progressively increased to the limits noted previously.

In the chronic setting, an initial empiric dwell time of 1 hour is often used in infants, although consideration has to be made for clearance of larger molecules, which would be favored by longer dwell times. Phosphate removal is less of a consideration in these patients compared to older children, as neonates and infants characteristically receive formula with a low phosphorus content or breast milk and may actually require supplemental phosphorus. As in older children and adults, the final determination of dwell time should take into account the characteristics of the individual's peritoneal membrane via standardized testing of solute transport capacity (peritoneal equilibration testing), as well as clinical and laboratory measures of dialysis adequacy.

As in the acute setting, the choice of PD solutions is largely dependent upon their availability. Despite the lack of firm data, there is a concern that the standard lactate-buffered solutions with glucose may have negative consequences on long-term membrane performance due to their low pH and the presence of glucose degradation products (GDPs). Given that these patients have many years of ESKD therapy in their future, the use of the new, more biocompatible dialysis solutions may prove to be particularly beneficial to the pediatric patient population. Data in neonates and young children on the subject is very limited (see Canepa et al. for a recent review).

Icodextrin (brand name Extraneal), a colloidal osmotic agent that is employed in PD solutions in place of dextrose is available in the United States but is rarely used in infants. Whereas Boer et al. showed that in 11 children (median age 10.3 years), a 12-hour exchange with 7.5% icodextrin produced ultrafiltration comparable to a 3.86% dextrose solution, Dart et al. reported poor ultrafiltration in very young children (median age 2.8 years) with its use. This poor efficacy was due to enhanced absorption of icodextrin across the peritoneal membrane, with half of the patients showing substantial absorption, even when dwell times were reduced from 10 to 6 hours. Van Hoeck also noted that the use of a long exchange with icodextrin could place a child into a negative amino acid balance.

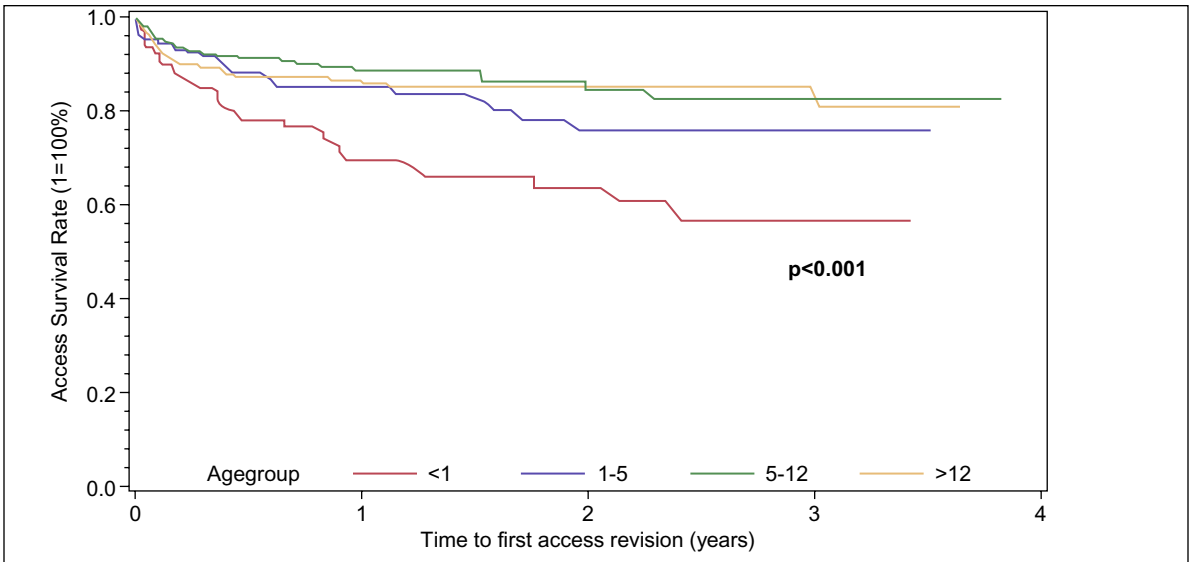
It can be difficult to precisely determine the efficiency or "adequacy" of dialysis with chronic PD in children. Although small molecule clearance measurements in the form of urea kinetic modeling (Kt/V_{urea}) are widely used, it must be emphasized that the current National Kidney Foundation KDOQI guidelines on PD adequacy, which recommends a total Kt/V_{urea} of ≥ 1.8 for children, is largely opinion based. Because a large, prospective study correlating solute removal and clinical outcome in pediatric patients treated with PD has not been conducted, care must always be taken to individualize therapy, even in cases of "adequate" or even high urea clearance. This is particularly true for the neonatal/infant patient population. Parameters that should be taken into consideration include linear growth and weight gain, increase in head circumference, and neurocognitive/psychomotor development. A recent guideline publication of the ISPD highlighted additional parameters that need to be considered in order to provide high-quality PD. These included attention to maintaining adequate volume status and effective blood pressure control.

An additional qualitative target of dialysis adequacy in the neonate and infant is the avoidance of hypovolemia and sodium depletion. Infants receiving PD experience excessive sodium losses across the peritoneal membrane due to the need for high ultrafiltration rates in relation to body weight. This can be compounded by losses of urinary sodium in patients with renal tubular disorders. Both breast milk and standard formulas contain 7–8 mmol of sodium per liter, which is inadequate for the replacement of ongoing losses. Without adequate supplementation (~3–5 mEq/kg per day), the consequences of the resultant hyponatremia and low intravascular volume can be catastrophic and include both blindness due to anterior ischemic optic neuropathy and cerebral edema. Finally, both sodium and protein losses can have a negative impact on growth. Specifically, neonates and infants can experience excessive losses of protein via PD, with studies demonstrating average losses of 250 mg of protein per kilogram of body weight or almost twice the peritoneal protein losses seen in older children. In order to avoid the negative consequences of protein depletion, current guidelines recommend a dietary protein intake of at least 1.8 g/kg/day for the first 6 months of life, taking into account the dietary reference intakes (DRIs) and peritoneal losses. Of note, protein losses can be higher with the use of alternative PD regimens such as tidal PD.

Outcome in End-Stage Kidney Disease

Even with surgically placed Tenkhoff catheters, chronic catheter survival remains suboptimal. Data from the Italian PD registry reported a 50% 1-year catheter survival rate in patients less than 6 months of age and an 83.7% 1-year catheter survival rate for those 6–24 months of age. Recent data from the IPPN Registry showed an overall catheter survival of 80% and 60% for patients > 1 year and < 1 year of age, respectively (Fig. 77.1). Infectious complications, including exit-site infections and peritonitis, also occur at a higher rate in neonates and infants. While peritonitis rates for patients 0–2 years of age have improved from a rate of 1 to 0.79 episodes per patient year over the last decade, they remain higher than the rate of 0.6 episodes per patient year seen in older children.

Most importantly, whereas mortality data have improved in children on dialysis over the past few decades, the highest



Number of Patients at Risk	Study Start	1 Year	2 Years	3 Years
< 1 year	124	48	23	10
1 to 5 years	144	64	35	10
5 to 12 years	261	119	49	29
>12 years	295	134	56	21

• **Fig. 77.1** Access survival in 824 incident patients according to patient age at catheter insertion. The survival rate was significantly lower in infants compared with patients in the older age groups ($p < 0.001$).

mortality rates are experienced by those patients who receive PD during the first year of life. The most recent NAPRTCS results, based on data collected from 2000–12, show a 3-year overall patient survival of 82.5% for patients who initiate dialysis during the first year of life. In comparison, children age 2–5 years at dialysis initiation have a higher overall survival rate of 92% at 3-year follow-up, and those over age 12 years have a survival rate of nearly 95%. Data from four separate international registries showed a combined slightly lower survival rate for those patients who initiated dialysis within the first month of life, with 2- and 5-year survival rates of 81% and 76%, respectively. A recent review of the USRDS database of 574 neonates and 1149 older infants (< 1 year) who received continuous peritoneal dialysis (CPD) showed improved survival in the latest era (2000–14) analyzed, with a patient survival of 86.8% and 74.6% among those who initiated dialysis as neonates at 1 and 5 years, respectively; comparable data for infants were patient survival rates of 89.6% and 79.3%, respectively. What persists, however, is the finding that the most important predictor of mortality in this PD patient age group remains the presence of nonrenal disease. Wood et al. clearly showed that comorbidities such as anuria and pulmonary hypoplasia were associated with the greatest risk of mortality in infants undergoing dialysis. A recent publication of the IPPN examining 1830 patients aged 0–19 years found that the presence of at least one comorbidity was associated with a 4-year survival of 73% versus 90% survival in those without a comorbidity ($p < 0.001$). Data on the influence of comorbidities on survival is likely impacted by regional differences as countries with a lower gross national income appear to be more restrictive in terms of making PD available to very young patients and those with significant extrarenal complications.

Conclusion

The last two decades have witnessed tremendous advances in the care of the neonate/infant requiring renal replacement therapy. PD, due to its simplicity and effectiveness, remains a popular modality for neonates with severe AKI and is the dialytic modality of choice when treating neonates/infants with ESKD. There have been notable improvements in patient survival, although complications remain high, especially in those infants with comorbidities. All of these issues highlight the need for a multifaceted approach to care to minimize or prevent complications and, in turn, promote growth, development, and readiness for transplant.

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Dialysis for Inborn Errors of Metabolism

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Inherited dysfunction of amino and organic acid metabolism usually manifests in the early neonatal period by neurologic abnormalities such as irritability, somnolence, and, eventually, coma. In urea cycle defects or organic acidemias, these symptoms are mainly due to excessive hyperammonemia, which may cause irreversible neuronal damage. In disorders of branched-chain amino acid metabolism such as maple syrup urine disease (MSUD), prolonged accumulation of leucine and/or its metabolites (2-ketoisocaproic acid) may lead to severe permanent neurotoxicity.

During the past 3 decades, the prognosis of these previously lethal disorders has been considerably improved by the introduction of several therapeutic principles.

1. The de novo synthesis of toxic metabolites can be suppressed by a high caloric supply inducing a state of anabolism and reduced proteolysis.
2. In hyperammonemic disorders, new medications utilize alternative metabolic pathways to reduce neurologic effects. These include sodium benzoate, sodium phenylbutyrate, carbaglutamate, and various vitamins and cofactors.
3. Specific dietary modifications such as a diet low in branched-chain amino acids in MSUD.
4. Finally and most importantly, the accumulation of the small, water-soluble neurotoxic metabolites can be rapidly reversed by dialytic removal.

Because the brain damage induced by neurotoxic metabolites is directly correlated with the duration of exposure to the neurotoxic metabolites, neonatal metabolic crises are considered emergency dialysis indications requiring use of the most readily available and effective dialysis modality.

Currently available dialytic regimens include

- Peritoneal dialysis (PD)
- Intermittent hemodialysis or hemodiafiltration (IHD/IHDF)
- Continuous renal replacement therapy (CRRT) (including continuous arteriovenous hemofiltration [CAVH], continuous venovenous hemofiltration [CVVH], continuous arteriovenous hemodialysis [CAVHD], continuous venovenous hemodialysis [CVVHD])

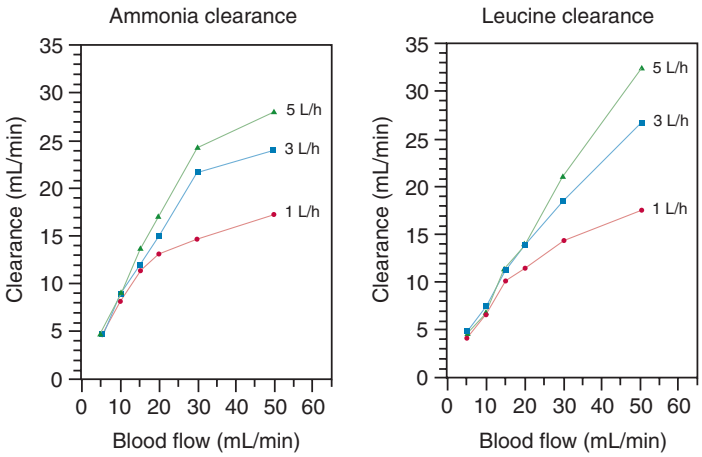
A large body of experimental and clinical evidence suggests that the clearance achievable by PD is much less than that obtained by HD. Historically, HD machines were not created for patients weighing less than 15 kg, which meant that for this unique population group, machines were often difficult to use, required large-bore central venous access, and were operated solely off-label. Because technological advances have improved the suitability of extracorporeal blood purification techniques for neonates, they are now the therapy of choice in appropriately equipped and experienced centers. In 2012, the Cardio-Renal Pediatric Dialysis Emergency Machine (CARPEDIEM) was designed and had successfully performed CRRT for infants less than 3 kg. It offers the advantage of extracorporeal dialysis, as well as additional advantages of smaller venous access down to 4 Fr, without sacrificing clearance or causing hemolysis. In addition, the accurate flow monitoring provides benefits to patient safety, although large-scale randomized controlled trials are not available to demonstrate advantages in survival neurological sequelae.

Although extracorporeal dialysis remains the treatment of choice, PD remains an alternative in cases where extracorporeal dialysis is contraindicated. Continuous-flow PD has been introduced as a method to improve clearance rates in PD and to more effectively dialyze neonates, although it is still not a mainstream technique used.

Techniques of Metabolite Removal

In patients with MSUD, the low endogenous clearance of leucine and other branched-chain keto and amino acids (BCAAs) is insufficient to reverse the accumulation of BCAA that occurs during catabolic states. BCAA clearances several times above the endogenous disposal rate are achieved with PD, and continuous extracorporeal blood purification techniques yield two- to threefold greater metabolite removal rates than PD. Although CVVH, CVVHD, and continuous venovenous hemodiafiltration [CVVHDF] have all been shown to be feasible, only HD has demonstrated a significant reduction of dialysis time requirements in comparison to PD.

In *hyperammonemic* metabolic crises, experimental evidence suggests that ammonium is more efficiently removed



• **Fig. 78.1** Effect of blood and dialysate flow rate on ammonium and leucine removal by hemodialysis in a neonatal setting.

by extracorporeal techniques than by PD. Clinical studies have shown that normalization of blood ammonium levels usually cannot be achieved in less than 24 hours by PD, and dialysis is typically required for 2–5 days. CVVH usually reduces blood ammonium concentrations by 90% within 10–12 hours. The most efficient toxin removal method is clearly achieved by CVVHD. The superiority of CVVHD over CVVH is evident from the fact that ammonium clearance with CVVH cannot be greater and is usually considerably less than the *plasma* flow rate through the dialyzer. In contrast, an ammonium clearance close to dialyzer *blood* flow can be achieved by CVVHD, as shown in Fig. 78.1. IHD reliably decreases blood ammonium concentrations by 75% within 3–4 hours. However, repeated sessions are frequently required because of residual or rebound hyperammonemia. Moreover, the use of IHD in neonates and young infants is usually limited by the size of the extracorporeal volume and the rapid depletion of other small solutes such as phosphate. Hence, CVVHD until complete normalization of blood ammonium levels should be considered the treatment of choice when very high dialysate flow rates can be ensured. When not possible, a combination of first IHD followed by CVVHD as maintenance therapy is recommended.

Extracorporeal Blood Purification

Dialysis Equipment

Catheter

The choice of the catheter has to draw a balance between the aim of achieving an adequate blood flow and the risks of catheter insertion in a newborn. Ideally, a blood flow of 150 mL/min/m^2 should be attained, that is, 30–35 mL/min in the mature neonate. This goal can be reached by inserting a 6.5-Fr double-lumen catheter (e.g., Gambro 6.5 Fr, 3.5 in) into the internal jugular or a femoral vein. This catheter size provides excellent blood flow rates (i.e., 30–40 mL/min), but insertion may be difficult in small neonates. Alternatively, two 5-Fr single-lumen catheters (e.g., Medcomp 5 Fr, 3.0 in) can be inserted in different femoral or jugular veins. Although umbilical catheters are unsuitable for dialysis because of their high flow resistance, 6.5-Fr hemodialysis (HD) catheters have occasionally been inserted into an umbilical vessel in neonates within the first few postnatal days.

4-Fr double-lumen catheters have been used successfully with the CARPEDIEM machine (see later) to dialyze infants of less than 3 kg body weight. However, the efficacy of the system for ammonia clearance has not yet been reported.

Dialyzer

Polysulfone dialyzers are preferred because of their superior biocompatibility and lower anticoagulation requirements. The surface of the dialyzer membrane should approximately match the body surface area of the patient. In neonates, we have had excellent experience with the Spiraflo HFT02 (Bellco, Mirandola, Italy) and the FX-Paed (Fresenius Medical Care, Bad Homburg, Germany) filter, which have to fill volumes of 19–24 mL at surface areas around 0.24 m^2. In larger infants, the Fresenius F3 (28 mL fill volume, 0.4 m^2 surface area) is recommended (Fresenius Medical Care, Bad Homburg, Germany). Current available dialyzers for neonates are summarized in Table 78.1.

Dialysis Device and Tubing

In principle, emergency dialysis in neonates with inborn errors of metabolism can be performed using adjusted tubing systems on standard HD machines, such as the neonatal tubing for the Fresenius 2008 or 4008 devices. These tubing sets have a fill volume of 47 mL. Even when used with a neonatal dialyzer such as the Spiraflo HFT02, the total volume of the extracorporeal system is 72 mL, which exceeds 10% of the estimated blood volume of an average neonate. Another disadvantage is that an incorrect blood flow rate is displayed when small-volume neonatal tubes are used. Moreover, as a result of the fixed high dialysate flow rate of 300–500 mL/min, critical depletions of phosphate, amino

TABLE 78.1 Commercially Available Filters for Neonatal CRRT: Main Characteristics

Filter	Manufacturer	Surface (m^2)	Membrane	Priming (mL)
Miniflow 10	Gambro-Lundia	0.045	AN69	3.5
Minifilter	Minntech	0.07	Polysulfone	6
CARPEDIEM 1	Bellco	0.075	Polysulfone	27.2 (circuit)
CARPEDIEM 3	Bellco	0.245	Polysulfone	41.5 (circuit)
HF20	Gambro-Lundia	0.20	AN69	60 (circuit)
FX-paed	Fresenius	0.2	Polysulfone	18

CRRT, Continuous renal replacement therapy.

acids, and other solutes not present in the dialysis fluid may occur with prolonged use of this technique.

Devices designed for continuous renal replacement treatment are better suited for acute dialysis in children. When considering the choice of a device in a neonate, the extracorporeal volume and accurate flow controls are important. Given the small blood volume of small neonates, volumes larger than 10% estimated blood volume (80 mL/kg) require circuit priming with blood. With very low flow rates, the percentage of error of a few milliliters per minute can be disastrous and cause unforeseen fluid overloading or shock. Current available devices are compared in Table 78.2.

Anticoagulation

Heparin has traditionally been the anticoagulant of choice, and the doses required are at 1000–2000 E/m^2 with a continuous infusion of 400 E/m^2/h during dialysis. Activated coagulation times (ACTs) of 140–200 seconds are targeted, monitoring it hourly. With the further increased risk of intraventricular hemorrhage in small neonates, regional citrate anticoagulation (RCA) has become a popular choice to anticoagulate the circuit. In order to set it up, a separate central venous line is required for calcium substitution. Our center is currently using a 3% ACD-A solution and a 10% calcium gluconate solution as the calcium substitute. Care must be taken not to replace the calcium via the postfilter circuit as this can lead to circuit clotting. Initial formulae to calculate rates of citrate and calcium replacement are as follows:

$$\text{Citrate flow rate (mL / h)} = \text{blood flow rate (mL / min)} \times 2$$

$$\text{Calcium flow rate (mL / h)} = \text{blood flow rate (mL / min)} / 4$$

The target ionized calcium levels are 0.20–0.30 mmol/L (0.8–1.2 mg/dL) in the postfilter circuit and within the normal range for a patient 1.1–1.3 mmol/L (4.4–5.2 mg/dL). Adjustments of 25% are made when the calcium levels are not within target levels with rechecking after 5–10 minutes of adjustment. Care must be noted that adjustments will more likely be needed in the neonatal circuits because of the increased circuit citrate required consequent to blood priming and also immaturity of the liver function due to age and the metabolic disease.

TABLE 78.2 Main Commercially Available Monitors for Pediatric and Neonatal CRRT: Main Characteristics

Monitor	Manufacturer	Pediatric Lines	Neonatal Lines	Total Extracorporeal Volume (mL)*	Blood Pump Range (mL/min)	Blood Flow Step-by-Step Increase (mL/min)	Fluid Turnover Range (mL/h)
Prismaflex	Gambro-Lundia	Y	–	60	20–100	2	50–2500
Multifiltrate	Fresenius	Y	–	72	10–100	2	10–7000
Aquarius	Baxter	Y	–	82	10–200	2	50–11,000
Plasauto Sigma	Asahi	Y	Y	70–87	1–400	1	10–12,000
CARPEDIEM	Bellco	Y	Y	27–42	2–50	1	10–300

*Prismaflex equipped with HF20 circuit, others with FX-Paed.
CRRT, Continuous renal replacement therapy.

Management Guidelines

Blood flow should be set to the maximal value operated by the machine to achieve maximal treatment efficacy without stimulating alarms, which should be set as wide as possible. The dialysate flow rate required to achieve maximal clearance is determined by the blood flow rate achieved. In a neonatal dialysis simulation study using a Spiraflo HFT02 filter, we found a linear relationship between blood flow and ammonium and leucine clearance up to the maximal blood flow rate usually achievable in neonates (i.e., 30 mL/min) with a dialysate flow rate of 5 L/h (see Fig. 78.1). As a rule of thumb, extraction of these metabolites is maximal when dialysate flow exceeds blood flow by at least a factor of 2. This target can easily be achieved by passing bag dialysis fluid along the filter utilizing the filtration/substitution pump system of a pediatric CRRT device equipped for high dialysate flow rates, such as the Asahi Sigma Plasauto. If only CRRT devices with lower maximal dialysate flow rates are available, an initial period of intermittent HD with 300-mL/min dialysate flow rate should be provided, optionally switching to CVVHD or CVVH once ammonium levels have decreased to a less toxic range. The dialysis fluid should contain glucose and potassium at plasma concentrations, and serum phosphorus levels should be monitored closely.

During treatment, dialysis efficacy can be monitored by measuring metabolite clearance using the formula:

$$\text{Clearance}\,(\text{mL/min}) = \text{bloodflow}\,(\text{mL/min}) \times (C_{\text{pre}} - C_{\text{post}})/C_{\text{pre}},$$

where C_{pre} and C_{post} are the pre- and postdialyzer metabolite blood concentrations.

The major complications to consider when dialyzing neonates or small infants with metabolic crises are clotting of the extracorporeal system and hemodynamic instability, each of which can cause treatment interruptions and, hence, hazardous delays in the removal of toxic metabolites. To prevent this, heparin or RCA is recommended as described previously.

Heparin should be administered at a dose sufficient to increase the ACT to 120–150 seconds to prevent clotting. We use an initial bolus of 1500 IU/m^2, followed by a continuous infusion of 300–600 IU/m^2/h. Anticoagulation should be monitored by hourly ACT measurements. Coagulation requirements are inversely related to the blood flow rate.

Hypotensive episodes and osmotic dysequilibrium occur less frequently than in neonates and infants dialyzed for renal failure because dialysis is usually isovolemic, and the accumulated metabolites are osmotically less active than the urea accumulated in uremia. However, hemodynamic instability is common in patients with prolonged duration of hyperammonemia because of urea cycle disorders but can be minimized by prefilling the system with blood and using appropriate extracorporeal tubing and dialyzer membranes with a total fill volume as small as 35 mL.

Whereas heating of dialysis fluids and bloodlines is generally required in neonatal dialysis to prevent hypothermia, therapeutic cooling to 34°C core temperature has been applied successfully to attenuate ammonia generation in neonates with metabolic crises. Whether this novel therapeutic concept will result in reduced dialysis need and improved outcomes remains to be proven.

HD should be continued until clinical improvement and complete normalization of the accumulated metabolite levels (ammonium, leucine) have been achieved. Because unknown amounts of pharmacologic scavengers are cleared by highly efficient extracorporeal blood purification, supplemental doses of these substances may be required during or after IHD.

Peritoneal Dialysis

Because of the lower toxin clearance, PD is generally not recommended and should be considered only when extracorporeal techniques are prohibited by vital sign contraindications or technical limitations.

Catheter

Stylet catheters can be placed immediately but bear a high risk for the subsequent development of leakage or outflow obstruction. Catheter leakage requires a reduction of dwell volumes or catheter replacement, and outflow obstruction may result in an increased intraperitoneal residual volume, both causing a further decrease of the peritoneal clearance. Thus, careful catheter insertion is a prerequisite for successful PD, and a slight delay for surgical implantation of a single-cuff Tenckhoff catheter may be justified.

Dialysis Prescription

Prescription of fill volumes must be balanced between maximizing toxin removal and adverse effects of increased intraperitoneal pressure (respiratory problems, catheter leakage). 15–30 mL/kg body weight appears to be an adequate compromise. Short dwell times (30–60 minutes) increase metabolite clearance but also ultrafiltration rates. The use of bicarbonate-buffered dialysate solutions, commercially available in many countries, may help to stabilize acid-base balance and prevent lactic acidosis in neonates.

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Neurocognitive Function in Pediatric Dialysis

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Introduction

Children with chronic kidney disease (CKD) present unique clinical challenges to practitioners when compared to adults in two very important aspects. First, they differ with respect to physical growth. Linear growth occurs through childhood and continues into puberty. Second, the human brain undergoes a remarkable physical and functional transformation from the moment of birth until early adulthood, with about 50% of brain growth noted in the first year of life alone. These facts present two challenges in the care of children with CKD, including end-stage renal disease (ESRD):

1) The sequelae of CKD/ESRD (uremia, anemia, acidemia, hypertension, mineral bone disorder) interfere with physical and brain growth.
2) As children with CKD/ESRD are growing up, they are exceptionally dependent on their care environment for their basic physical and emotional needs, nutritional requirements, educational support, and for their health care.

This chapter is a focused review of evidence related to CKD/ESRD and its effect on the neurocognitive growth and development of children.

Chronic Kidney Disease and Its Effects on Childhood Neurocognitive Development

Background

The association between neurologic dysfunction and kidney disease was recognized over 40 years ago when a correlation between the frequency of slow waves on EEG and serum creatinine was first described in adults with kidney failure.[1] A decade later, numerous studies demonstrated that up to 65% of children with CKD show signs of developmental delay.[2] The subsequent recognition of neurocognitive effects of aluminum-induced neurotoxicity was so important that it led to major modifications in the treatment regimens of these patients and resulted in the elimination of an important confounder in the relationship between CKD, its therapy and neurocognitive abnormalities. As management of neonatal and childhood-onset CKD with dialysis and renal transplant improved survival in children significantly, the presence and clinical significance of early-onset neurocognitive deficits in these patients became increasingly apparent.

It is well known that any chronic or significant clinical illness, including CKD, can seriously disrupt the normal process of neurocognitive development seen in children. However, kidney disease may represent a unique subset of chronic illness that leads to a profound impact on childhood neurocognitive development when compared to some other conditions. A systematic review of studies reporting the magnitude of the impact of chronic illness on neurocognitive development looked at children with cystic fibrosis, hemophilia A, ESRD, and end-stage liver disease. It showed that children with cystic fibrosis and hemophilia A did not appear disadvantaged by their illness when compared to children with chronic liver and kidney disease. The authors concluded that despite optimal management, the latter two cohorts show a mild cognitive deficit when compared to population norms.[3]

Risk Factors

Not only is the uremic milieu unique in its ability to produce acute changes in mental status and cognitive functioning, but also numerous studies have demonstrated clinically a significant neurodevelopmental delay in children with CKD. The concurrent presence of severe electrolyte abnormalities, chronic metabolic acidosis, uncontrolled hypertension, renal osteodystrophy, chronic anemia, and malnutrition in CKD has a significant impact on growth and neurodevelopment in children. Other contributing risk factors include the age of onset of renal disease, the duration of illness, presence of genetic or chromosomal disorders, multisystem disease, the need for renal replacement therapy (RRT), as well as the modality used and the psychosocial environment at home.[4] This was demonstrated in a

study of 29 children with CKD, which showed that significantly lower IQ and memory function was associated with increased severity of disease, longer duration of illness, and younger age at onset.[5]

Spectrum of Neurocognitive Abnormalities

The neurodevelopmental abnormalities associated with renal disease can range from severe disorders including seizures, hyper- and hypotonia, myoclonus, dyskinesia, microcephaly, and profound neurocognitive delays, to more subtle changes such as sleep disturbance, poor school performance, and changes in memory and executive function.[6] In infants and toddlers who develop CKD at an early age, delays have been reported in both motor and cognitive domains.[4] Studies have estimated that about 25% of patients of infants and toddlers who develop severe renal disease will demonstrate evidence of various developmental delays.[7] In addition, in a prospective cohort study of 319 children with CKD, low total academic achievement was seen in about one-third of the children, with mathematics having the lowest distribution of achievement scores.[8] Additionally, up to a third of children may experience various forms of sleep disturbances, including restless leg syndrome, insomnia, and excessive daytime somnolence.[9]

Measures of Neurocognitive Function

A case-control study of 20 children with CKD revealed an IQ difference of almost 23 points (89 vs. 112) when compared to age-matched healthy controls. Children with CKD also performed poorly in this multivariate analysis after controlling for chronological age and IQ, in specific testing performed for memory functions as well as executive function domains. The authors also report that patients with CKD demonstrated significantly lower memory abilities when compared with age-matched controls with respect to short-term visual memory, short-term verbal memory, as well as new learning.[4] Deficits in verbal abstraction abilities, visual-motor abilities, memory scores in tasks requiring immediate recall, and sustained attention skills have also been reported in patients with CKD when compared to control groups.[10]

The presence of these abnormalities may be subtle and possibly go unrecognized, leading to poor school performance. It is very important to consider formal testing in patients with CKD to optimize their neurodevelopment potential and educational performance and create realistic expectations about their abilities.

Psychiatric Disturbances

Gledhill and colleagues define psychiatric morbidity as the presence of handicapping abnormalities in behavior, relationships, and emotions that impair personal as well as social functioning.[11] The presence of short stature, malnutrition, growth retardation, delays in sexual maturation, and scars from dialysis access or arteriovenous (AV) fistulas all may contribute to a poor body image and low self-esteem in children with CKD. The prevalence of depression in children with CKD has been reported to be from 7% to 35%.[12] A lower level of maternal education was identified as a risk factor for depression in a large cross-sectional population from the Chronic Kidney Disease in Children (CKiD) study. The study also showed that the presence of depression was associated with a worse quality of life (QoL).[13] A cross-sectional analysis of depression and neurocognitive outcomes in children, adolescents, and young adults (ages 8–25) compared 71 participants with CKD with 64 controls. Depression was identified in 17% of patients with CKD and was not significantly different from controls (12.5%). The study also found that in the CKD cohort, patients who were obese were significantly more likely to be depressed.[12]. Another study looked at 19 predialysis patients and 19 patients on hemodialysis. The overall prevalence rate of psychiatric diagnoses in all 38 patients was 52.6%. Adjustment disorders (18.4%), depression (10.3%), and neurocognitive disorders (7.7%) were the most common abnormalities noted. These disorders were significantly more common in the dialysis population (68.4%) compared to predialysis patients (36.8%). The authors did not find any association between the presence of a psychiatric disturbance and gender, anemia severity, duration of kidney disease, and the duration or efficiency of hemodialysis therapy.[14]

Children with CKD remain at significant risk of neurocognitive and psychiatric disturbances related to their primary disease as well as social and emotional risk factors. Recognition, evaluation, and treatment of these potentially serious comorbid conditions remain important parts of their management.

Neurocognitive Issues in Children on Dialysis

Background

ESRD and its treatment pose many challenges to normal childhood development. Even when managed according to standards of care, children on dialysis have hemoglobin levels lower than those of healthy children. Changes in the plasma/brain osmotic gradient during dialysis treatments carry a risk of cerebral edema. The uremic milieu itself has adverse consequences on brain functioning. High blood pressure, which frequently accompanies ESRD, has adverse neurocognitive effects of its own. Relative hypotension during dialysis treatment transiently compromises cerebral perfusion. Blood pressure medication can impair cognitive functioning.

There are also social and environmental sequelae of dialysis that create barriers to a child's optimal neurocognitive functioning. Missed school due to medical appointments and treatments interfere with academic achievement. Social isolation and accompanying depression or anxiety make

normal developmental tasks more difficult to accomplish. Child and parent attention to dialysis needs can divert attention from school engagement, sports, and social activities, all of which are beneficial to a child's neurocognitive development.

Neurocognitive functioning in children is complex and nuanced. Assessment tools exist to measure global intellectual functioning (IQ), specific cognitive processes, academic achievement, and task-oriented abilities. Therefore, categorizing the wide range of neurocognitive sequelae of dialysis involves compiling data from a wide variety of neurocognitive assessment methods.

Measures of Intelligence and Cognitive Functioning

Early studies documented a high prevalence of low intellectual functioning among children with renal failure.[15,16] Fortunately, the magnitude of this effect seems to have lessened in recent decades, likely attributable to advances in the supportive care of children with ESRD.

Among 62 children with ESRD, scores on the Test of Non-Verbal Intelligence were consistently lower than sibling controls. Children with ESRD scored in the 27th percentile, while their siblings scored in the 32nd percentile. This finding held true for both dialysis patients and posttransplant patients.[17] Bawden et al. found a difference in Full-Scale Intelligence Quotient of 10.9 points between children with pretransplant ESRD and their sibling controls.[18]

When looking at measures of cognitive function in children on dialysis, it is necessary to look for both cognitive challenges from an underlying diagnosis and cognitive challenges arising from kidney dysfunction and its treatments. Among 1830 children on peritoneal dialysis enrolled in the International Pediatric Peritoneal Dialysis Network (IPPN), 283 (15.5%) were identified as having cognitive impairment. One caveat is that 84 of the children with cognitive impairment also had a genetic syndrome, which impacted their cognitive functioning. Of the nonsyndromic children in this cohort, 199 of them (11.8%) had cognitive impairment, a proportion much higher than expected in a nondialysis population.[19]

Among 12 children on hemodialysis in Mansoura, Egypt, full-scale IQ was 29.5 points lower than in 12 healthy children drawn from the same population (75.5 vs. 105). None of the children on hemodialysis attended school, median Kt/V was only 1.1, and mean hemoglobin was only 7.9 g/dL. It is certainly possible that more aggressive treatment of school absence, uremia, and anemia may have improved measures of cognitive functioning in these children.[20]

Given the rapid pace of neurodevelopment in early childhood, it has been hypothesized that early-onset ESRD is associated with the most severe neurocognitive sequelae. Johnson and Warady have demonstrated this among children diagnosed with ESRD in the first 16 months of life.[21] When those children were surveyed later in childhood, all measures of cognitive functioning were at least 1 standard deviation below population norms, with an average full-scale IQ of 76.8 (population mean, 100; SD, 15). Improved cognitive functioning was associated with older age at starting dialysis, shorter time on dialysis, and younger age at transplant. These patients also scored significantly below their siblings on the same assessments.

Popel et al. surveyed children who received a kidney transplant before their fifth birthday. They found that these children scored a full standard deviation below population averages for visual-motor integration, full-scale IQ, and everyday living skills. Poorer outcomes were associated with a longer time as a dialysis patient and with the use of hemodialysis (as opposed to peritoneal dialysis).[22]

Measures of Academic Achievement

Compared with their siblings, children with nonsyndromic ESRD had similar scores on tests of academic achievement, including reading, spelling, arithmetic, and reading comprehension.[18] This is despite a significantly lower IQ, lower scores of visual-motor integration, and lower fine motor coordination demonstrated in the same study.

Johnson and Warady studied children with ESRD in the first 16 months of life who showed significant deficits in academic achievement in middle childhood. Scores on Weschler Individual Achievement Tests were a full standard deviation below population norms on all domains tested. Lower achievement test scores were associated with younger age at dialysis initiation, longer time on dialysis, and older age at transplant. Compared with their siblings, these children had lower scores on achievement tests of word reading, numerical operations, spelling, and total achievement.[21]

Measures of Emotional Well-being

In a study of neurocognitive performance, Mendley and Zelko administered the Beck Depression Inventory and Children's Depression Inventory to nine subjects, both while receiving dialysis and after transplant. In this population, none of the patients met the criteria to diagnose depression.[23] Compared with their siblings, children with nonsyndromic ESRD had similar (lack of) symptoms related to behavior concerns and similar self-reported Global Self-Worth.[18]

The prevalence of sleep disturbances in children on dialysis is reported to be as high as 86%. Those disturbances include sleep-disordered breathing, restless leg syndrome/periodic limb movements, and excessive daytime sleepiness.[24]

When looking at human development over the life course, children treated for ESRD in the 1970s–90s appear to suffer from delayed achievement of adult milestones.[25] When young adults who had ESRD diagnosed in childhood were surveyed, they reported lower scores for autonomy development, psychosexual development, social development, and substance use/gambling. While these data are quite discouraging, it is reasonable to assume that such outcomes are better today, given advances in the delivery of RRT to children and supportive care for children with ESRD. There

is also a clear improvement in the cognitive performance of children with ESRD since the 1970s, which likely empowers greater adult achievement.

Improvements with Kidney Transplantation

The prevalent pediatric ESRD population in the United States in 2017 was 9667 patients. That includes 1608 hemodialysis patients, 977 peritoneal dialysis patients, and 7082 transplant patients.[26] For the majority of children on dialysis, dialysis treatments are simply a temporizing measure while preparing for a kidney transplant. One way to demonstrate the impact of dialysis on neurocognitive functioning is to perform assessments while receiving dialysis and after kidney transplants. Mendley and Zelko demonstrated that after transplant, children had improvements in their mental processing speed, decision speed, and accuracy of learning.[23]

In a study of prevalent hemodialysis, peritoneal dialysis, and transplant patients, child-reported QoL was similar for those receiving peritoneal dialysis and posttransplant. Parent-reported QoL (for the child) was best for transplant, followed by peritoneal dialysis, and worst for hemodialysis. Interestingly, patient-reported QoL was consistently higher than parent-reported QoL.[27]

However, a more recent study from northern Europe offered much bleaker data. In a survey of all prevalent ESRD patients in the Netherlands, Belgium, and Germany, children reported much lower mean QoL scores compared to healthy controls and compared to children with other chronic conditions.[28] The only domain of health-related QoL that was improved for transplanted children compared to children on dialysis was physical health. Scores were similarly low for emotional functioning, social functioning, school functioning, and psychosocial health. There was a suggestion in the data that with longer time on their RRT modality, children with a transplant reported lower QoL, while children on dialysis reported higher QoL. One thread that emerges from all QoL surveys of children with ESRD is that nonrenal comorbid disease is associated with lower QoL.

The conflicting data about QoL in children with ESRD and the impact of modality change highlight the importance of QoL assessment for individual patients. It is important to view information about neurocognitive functioning before and after dialysis dependence as part of a comprehensive assessment of child wellness that informs the care of individual patients.

Best Practices to Support Neurocognitive Function in Children With Chronic Kidney Disease and End-Stage Renal Disease

Children on dialysis miss out on schooling as part of their dialysis therapy. Strategies to minimize missed school can help maintain opportunities for education and social development that are critical to child wellness. These strategies include choosing home dialysis (over in-center treatments) whenever possible, scheduling medical appointments around school needs, and providing clear communication with schools about allowable activities. For children on in-center hemodialysis, scheduling one weekly treatment on the weekend lessens the number of school days interrupted for dialysis treatments. Pediatric nephrologists should partner with parents, social workers, and education professionals to advocate for the most meaningful educational resources for each child.

Given the high prevalence of neurocognitive deficits in children on dialysis, pediatric nephrologists should have a low threshold to refer these children for formal neurocognitive testing. This is especially true because measures of global intelligence, such as IQ, may not be sensitive enough to show subtle abnormalities in neurocognitive and neuropsychological function.[6] Recognizing the specific level of neurocognitive functioning in a child allows the nephrologist to individualize expectations related to self-care, independent medication administration, diet adherence, and overall illness experience. Formal neurocognitive testing also allows for a tailored educational plan to meet the needs of the child. Experts in the field have also proposed specific cognitive remediation programs as a promising treatment modality in the overall care of children with CKD and ESRD.[29]

Due to advances in RRT, survival in children with CKD and ESRD has improved tremendously. As these children progress from CKD to ESRD to transplant and possibly back to dialysis if a transplant fails, they have to face the looming challenges of future adulthood and independent living. Recognition, support, management, and treatment of their neurocognitive needs by pediatric nephrologists will allow these children to complete schooling, obtain gainful employment, meet family needs, and learn to successfully self-manage their lifelong illness.

Conclusions

As a group, children with CKD and ESRD face challenges to their neurocognitive growth and development. These are associated with measurable differences from non-CKD children in the domains of intelligence, academic achievement, mental health, and psychological and emotional well-being. Younger ages with ESRD diagnosis increased time on dialysis, and the use of hemodialysis (vs. peritoneal dialysis) are associated with greater neurocognitive challenges. Physicians who care for children with CKD and ESRD are tasked with recognizing and managing these barriers whenever possible. Furthermore, physicians who care for children with CKD and ESRD must remain strong advocates for their patients in order to help deliver the resources needed to optimize their cognition and neurodevelopment during their critical childhood formative years.

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Growth in Children With End-Stage Kidney Disease

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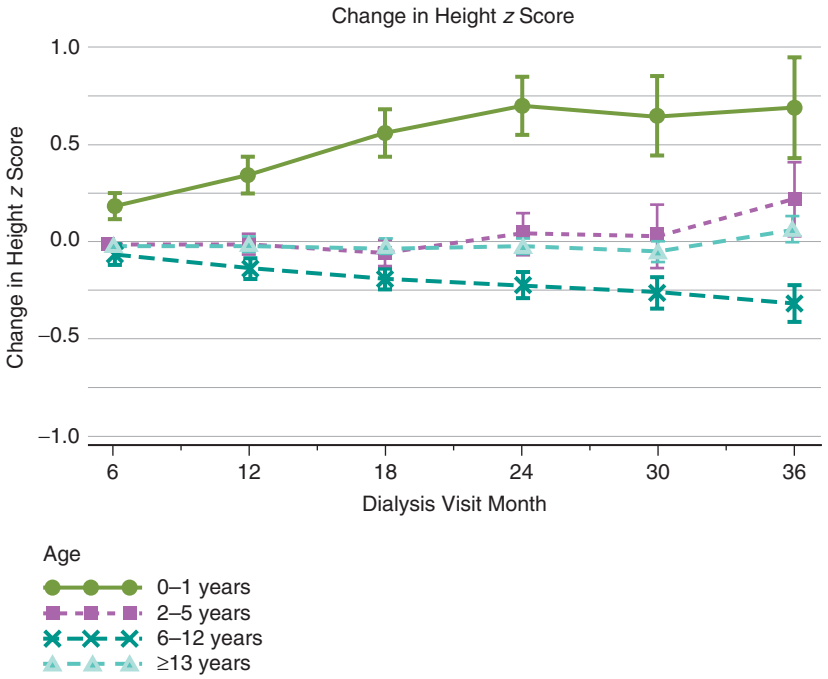
Introduction

Growth is a complex biologic process dependent on adequate nutrition as well as the integrated homeostasis of metabolic and endocrine pathways. Growth failure has long been recognized as one of the most common and profound complications seen in children with chronic kidney disease (CKD) and advances in our understanding of the crucial role of nutrition and benefits of treatment directed to the growth hormone-insulin-like growth factor-1 (GH/IGF-1) axis has expanded over the last two decades. Growth impairment may be seen in up to 50% of children with moderate to severe renal dysfunction (CKD 3–5). Despite available treatments, including renal replacement therapy, 30%–60% of children with end-stage kidney disease (ESKD) ultimately have reduced adult height. Data from the North American Pediatric Renal Trials and Cooperative Studies (NAPRTCS) 2011 annual report included 7039 patients and provided patient characteristics and height data for children at the initiation of maintenance dialysis. Baseline height scores for children at dialysis initiation were 1.60 standard deviation scores (SDS) below appropriate age- and sex-adjusted height levels. During the first 36 months of dialysis, mean changes in height SDS (z scores) for patients stratified by age continued to lag for all but children <2 years of age (Fig. 80.1), and the absolute height deficits were worse for younger patients and males. A more recent paper described a cohort of 732 German adults who had onset of ESKD in childhood, with 88% transplanted during childhood. Their mean adult height SDS was low at -1.80, and the majority qualified as having short stature as adults.

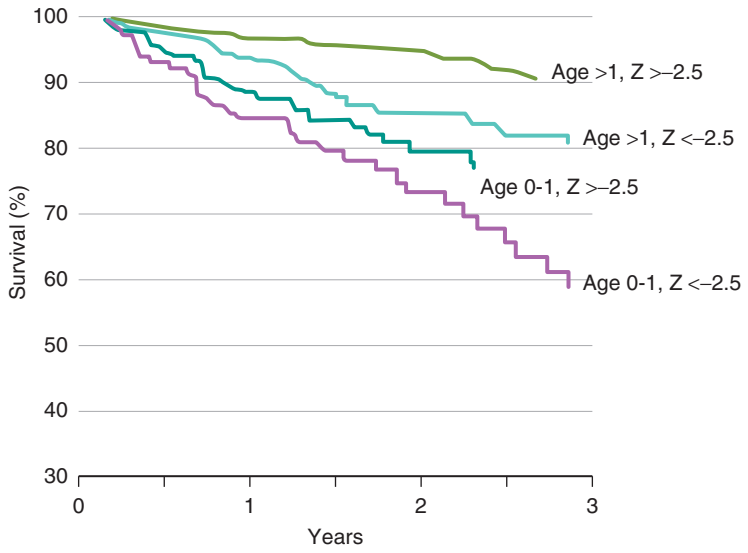
Although a trend toward improved final adult height for children with CKD has been noted over the last two decades, mean final height in several studies of adults who had CKD stage 3–5 in childhood still ranges between −0.6 and −3.5 SD. Children who required dialysis during childhood manifest the greatest adult impairment in height. This outcome is a significant burden for these young adult survivors of childhood CKD with long-term negative consequences on their adult quality of life (QOL), self-esteem, employment, and life satisfaction. Broyer et al. studied the social outcomes of 244 adults who had received kidney transplants as children with ESKD (mean age at transplantation 11.9 ± 4.0 years) and found that better adult height correlated with higher educational attainment, better employment rates, more successful marriages, and greater rates of independent living. Rosencrantz explored quality of life in 29 adults with the onset of ESKD in childhood who had low mean adult height SDS at –1.56 ± 1.55; 36% were dissatisfied with their adult height (compared with 4% of healthy controls), and their height dissatisfaction correlated with poorer quality of life.

Children receiving kidney transplants and/or treatment with recombinant human GH (rhGH) show better mean final height than those children who continue on long-term dialysis and/or did not receive concomitant rhGH therapy. Young age at onset of ESKD, long duration of renal failure, male gender, and the presence of congenital nephropathies are the most relevant risk factors for decreased final adult height in these survivors of childhood ESKD.

The multifactorial pathogenesis of growth failure in children with CKD complicates the approach to prevention and treatment. Congenital and acquired renal abnormalities can impact growth and development at variable time points, but congenital issues tend to affect growth in childhood more than acquired renal disorders. Moreover, clinical manifestations related to CKD can be highly variable and result in very diverse issues, including fluid and electrolyte abnormalities, metabolic acidosis, abnormal bone metabolism, and malnutrition, all of which can significantly affect growth. In addition, children with CKD undergo different medical interventions and modes of renal replacement therapy at important times during their growth and development. The most important factors that impact growth in children with CKD are the age of onset of CKD and its severity. The complexity of growth impairment, however, is ultimately related to (1) patient genetic factors and nonrenal comorbidities, (2) specific aspects of the timing, type, and severity of the underlying renal disorder, (3) specific types and severity of CKD complications, and (4) the impact of the different types and timing of renal therapies.



• **Fig. 80.1** Mean change in height *Z* score reported by age group during the first 36 months after dialysis initiation. (Reproduced from North American Pediatric Renal Trials and Collaborative Studies 2011 annual report. http://www.NAPRTCS.org.)



• **Fig. 80.2** Association of growth failure and survival in children with chronic kidney disease. (Reproduced from Furth SL, Hwang W, Yang C, Neu A, Fivush B, Powe NR. Growth failure, risk of hospitalization and death for children with end-stage kidney disease. *Pediatr Nephrol*. 2002;17(6):450-455.)

The impact of growth failure in children with CKD can be profound. In CKD, chronic malnutrition can lead to significant neurodevelopmental and behavioral issues such as irritability, apathy, attention deficits, and impaired developmental milestones and learning. Growth failure in children with CKD has been associated with an increased incidence of hospitalizations as well as a reported threefold increased risk of mortality after initiation of dialysis. Furth evaluated the risk of death in a cohort of 2306 patients with CKD from the NAPRTCS registry in 2002. Eligible patients (21 years or younger) who had height data at the initiation of dialysis Fig. 80.2 were stratified by standardized height (height *z* score $<$ or >-2.5) and age ($\leq$ or >1 years). Children with better height had lower risk of death than shorter children in both age groups. The burden of significant impairments in both psychosocial and psychological development as well as long-standing decreased QOL, are now recognized as major adverse outcomes in children with CKD who demonstrate growth failure, amplifying the need for prevention and early intervention to promote good growth in these children.

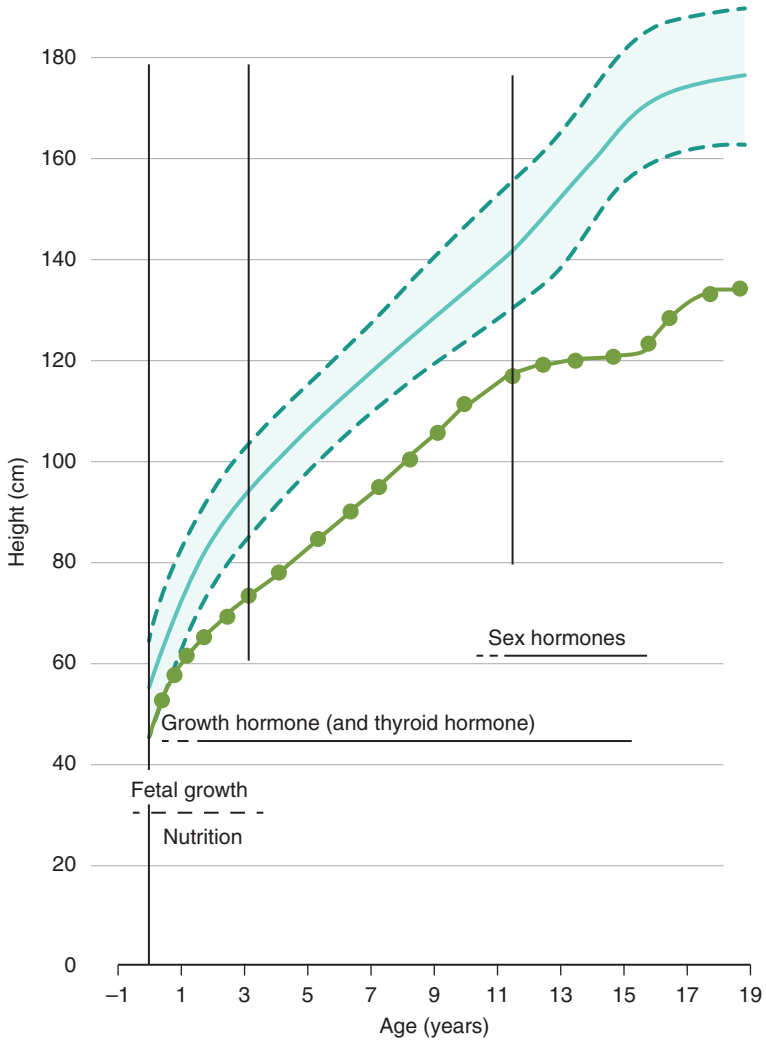
Growth Patterns

Physiologic growth patterns can be divided into the periods of infancy, mid-childhood, and puberty. Adequate nutritional intake is the most important requirement for growth during the first 2 years of life, where growth and neurologic development are more directly dependent on caloric intake than in older age groups. In mid-childhood, growth is greatly driven by the somatotropic hormone axis. During puberty, the gonadotropic hormone axis provides an additional influence on growth by stimulating growth plate chondrocytes, modulating GH secretion from the pituitary gland, and directly affecting all somatic cells. The growth pattern typically seen with congenital chronic renal failure and the sequence of primary growth factors are depicted in Fig. 80.3.

Children with congenital renal disorders, where renal impairment is present in the first two years of life, are particularly affected because an astounding 33% of final adult height is normally attained during the first 2 years of life. Growth progresses steadily through childhood but typically at a lower rate, and CKD during this period can have a profound impact over time. Height velocity again decreases during the last 2–3 years of prepubertal growth, resulting in further growth impairment. Height and weight velocity then accelerate during puberty, especially the first few years of puberty, and the impact of CKD during this period can be quite impactful, accounting for up to 12–18 inches less adult height than predicted for affected children with CKD. Reduced adult height is an all-too-common consequence of CKD-mediated growth impairment during childhood.

Assessment of Growth

Because growth failure is a common concern in children with CKD, anthropometric measurements must be incorporated into the routine care of these children. In fact, these anthropometric values should be considered as a *fifth vital*



• **Fig. 80.3** Typical growth pattern in congenital chronic renal failure. Relative loss in the nutrient-dependent infantile and gonadal hormone–dependent puberty phases and percentile-parallel growth in the mainly growth hormone–dependent growth period in midchildhood is shown. The *shaded area* represents the normal range, 3rd to 97th percentiles. (Reproduced from Schaefer F, Mehls O. Endocrine, metabolic and growth disorders. In: Barrat T, Holliday MA, Avner ED, eds. *Pediatric Nephrology*. Baltimore: Williams & Wilkins; 1994:1241-1286.)

sign for the child with CKD evaluated in the outpatient setting. Regular assessment of head circumference (until 3 years of age), height, weight, and body mass index (BMI) permits early detection of failing growth and provides opportunities for appropriate focused interventions. Height (length for children not standing yet), weight, and BMI must be measured and recorded at each routine health care visit. Plotting these values on age- and gender-appropriate growth charts and calculating percentiles and SDS allows detection of concerning measures or trends. Importantly, calculating height velocity SDS score facilitates detection of suboptimal growth before the height value is out of the normal range.

Growth failure is defined as height and/or weight below the third percentile (<−1.88 SDS) for age and gender. BMI below the third percentile (<−.88 SDS) for age and gender is also an important marker of growth failure. Although detection of height, weight, or BMI below −1.88 SDS is a clear sign of growth failure, earlier detection of a disturbing growth pattern (e.g., height velocity SDS <−1.88) can alert the care team to address the issues of growth in the affected child.

Growth Failure in Chronic Kidney Disease

There is no single cause of growth failure in most children with CKD; multiple factors often are in play (Table 80.1). Although genetic and nonrenal comorbidities exert significant effects on growth, the influence of nonmodifiable and modifiable factors ultimately defines the course of growth in children with CKD.

Underlying Renal Disease

The earlier in life CKD develops, the more likely the child is to have growth failure. Congenital renal dysplasia or hypoplasia, with or without urinary tract obstruction, is the most common cause of ESRD during infancy and childhood. Renal dysplasia is often associated with significant water and electrolyte losses, which can additively contribute to poor growth beyond the impact of uremia. Children with chronic glomerulopathies may show a decline in growth rates even with only mild renal insufficiency, in the presence of significant protein losses and/or glucocorticoid exposure. Among the various causes of renal disease, children with nephropathic cystinosis or primary hyperoxaluria show the most markedly compromised final adult heights, with their growth failure linked to the combination of proximal tubular dysfunction and uremia.

Protein–Energy Malnutrition

The most important cause of poor growth in children with CKD is inadequate energy and/or protein intake. Normal infants and children are particularly vulnerable to malnutrition due to their typical low nutritional stores and relatively high energy demands inherent in this phase of life. The presence of CKD can further complicate the ability of a young child to meet these essential needs. Protein-energy malnutrition is common in children on dialysis, with as many as one-third showing mild or moderate malnutrition and 1/10th severe malnutrition. The term "malnutrition–inflammation complex syndrome" (MICS) aptly describes the association between

TABLE 80.1 Factors Affecting Growth in Children With CKD

Genetic Factors/Birth-Related Factors	Nonrenal Comorbidities
• Parental height/genetic endowment • Gender • Syndromic conditions • Prematurity • Small for gestational age	• Neurologic disorders • Genetic conditions • Heart disease • Gastrointestinal/liver disorders • Pulmonary Disorders • Neoplasia/cancer treatments
Renal Nonmodifiable Factors	**Renal Modifiable Factors**
• Age of CKD onset • Level of GFR • Residual renal function • Type of renal disorder • Corticosteroid therapy	• Excessive water and/or salt losses • Poor caloric/protein intake • Malnutrition-inflammation syndrome • Metabolic acidosis • Anemia • CKD–mineral bone disorder • GH/IGF-1 resistance • Gonadotropin abnormalities

CKD, Chronic kidney disease; *GFR*, glomerular filtration rate; *GH*, growth hormone; *IGF-1*, insulin like growth factor 1.

chronic inflammation and malnutrition in children and adults with CKD contribute to MICS, including comorbid metabolic and inflammatory illnesses, uremic toxins, oxidative stress, anorexia, nutrient loss through dialysis, and induction of cytokines during exposure to bioincompatible dialysis materials.

Metabolic Acidosis

In children with CKD, metabolic acidosis usually develops as glomerular filtration rate (GFR) falls below 50% of normal due to accumulation of sulfates, phosphates, organic and amino acid breakdown products. In some children with CKD, metabolic acidosis is exacerbated by tubular losses of bicarbonate and impaired renal acid excretion. In the child with CKD, intake of protein and acid, as well as catabolism, also contributes to the degree of metabolic acidosis. Independent of contributing factors, metabolic acidosis is associated with decreased linear growth and increased protein breakdown in children with CKD. In experimental uremia models, metabolic acidosis suppresses GH secretion and reduces serum IGF-1 levels, triggers resistance to anabolic actions of GH, inhibits albumin synthesis, increases calcium efflux from bone, and augments protein degradation. Alterations of protein metabolism by metabolic acidosis in children with CKD also result in increased glucocorticoid production, which can further impair growth.

CKD–Mineral Bone Disorder

Skeletal disturbances due to CKD–mineral bone disorder (CKD–MBD, formerly termed renal osteodystrophy) can contribute to uremic growth failure. Abnormalities in bone cells and bone structure are part of both high and low bone turnover forms of CKD–MBD. Excessive secondary hyperparathyroidism can lead to destruction of growth plate architecture, epiphyseal displacement, and metaphyseal fractures, which can impair longitudinal growth. Growth arrest may also occur as a result of severe destruction of the metaphyseal bone architecture. More severe CKD–MBD derangements are associated with more profound growth delay.

Anemia

Long-standing anemia in CKD patients may lead to profound systemic consequences such as anorexia and catabolism due to altered energy metabolism. Anemia may suppress growth secondary to poor appetite, intercurrent infections, cardiac complications, and reduced oxygen supply to cartilage, and chronic anemia has been associated with delayed growth in children with CKD.

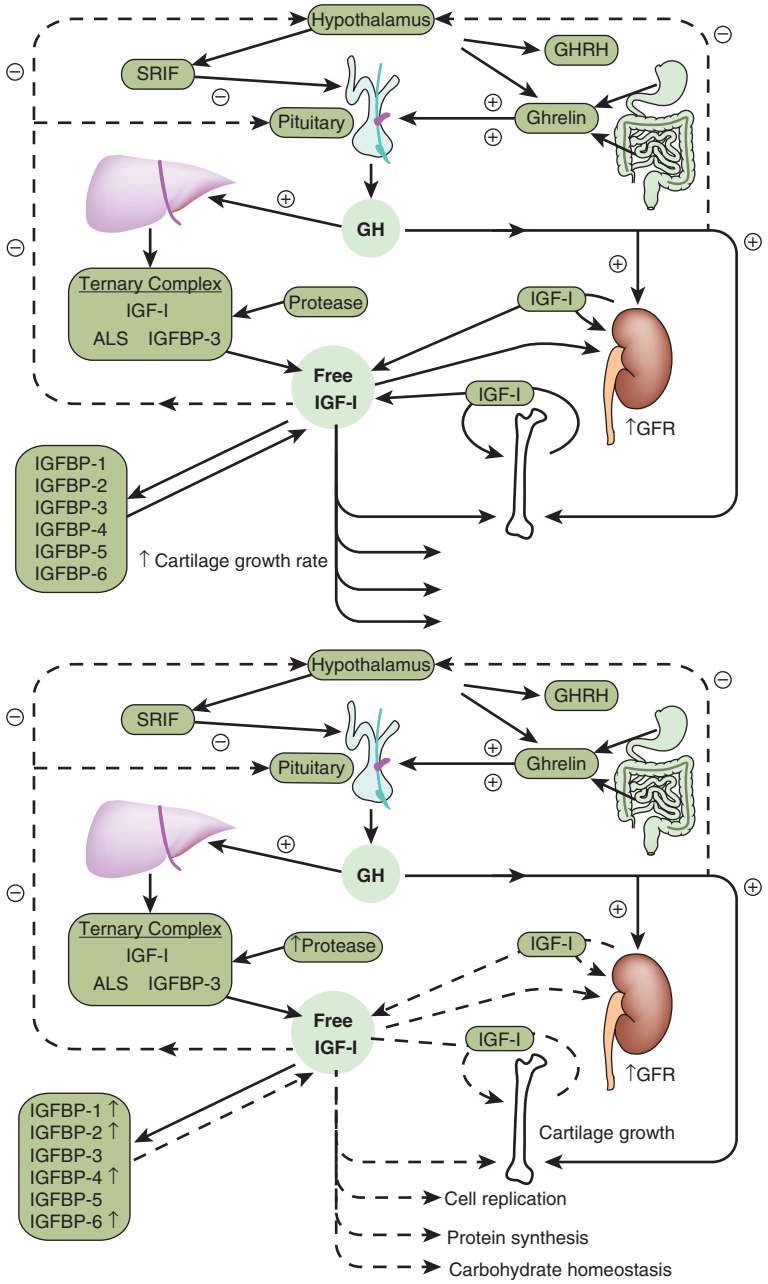
Endocrine Dysfunction

The GH–IGF-1 axis is an important regulator of growth and metabolism in children, and significant abnormalities in this axis occur in children with CKD (Fig. 80.4). In the normal state, GH production and release by the anterior pituitary are regulated by hypothalamic GH-releasing hormone and somatostatin, with circulating GH and IGF-1 providing negative feedback to the hypothalamus. Release of GH is also stimulated by the GH-releasing peptide ghrelin, which is secreted by enteroendocrine cells of the stomach and hypothalamus. Ghrelin helps regulate energy homeostasis through its effects on stimulating hunger/appetite and adjusting energy output; it also stimulates GH release to lead to increased growth and body mass. Circulating GH stimulates production and release of IGF-1, primarily from the liver. Most circulating IGF-1 is bound to IGF-binding protein (IGFBP) 3 and acid-labile subunit (ALS); less than 1% of IGF-1 in the circulation occurs in the free or bioactive form. Circulating free IGF-1 mediates many of the biological effects of GH, including stimulation of longitudinal bone growth and regulation of renal hemodynamics. GH and IGF-1 also have paracrine release and effects in addition to the more well-understood endocrine characteristics.

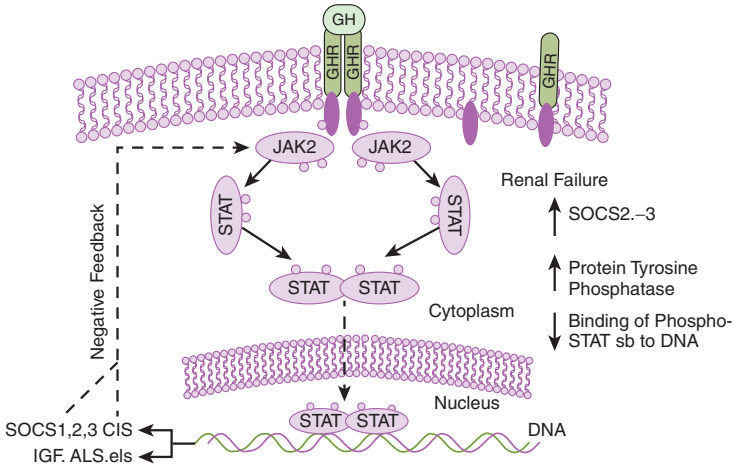
Children with CKD have multiple abnormalities of the GH–IGF-1 axis (Fig. 80.4). These include increased circulating levels of GH as a result of increased pulsatile release and reduced renal GH clearance, counterbalanced by reduced responsiveness to endogenous GH and IGF-1. Uremic GH and IGF-1 resistance impair many bone cell processes and can directly alter linear bone growth. An important mechanism for GH resistance in CKD involves defects in the postreceptor GH-activated Janus kinase 2 (JAK2) signal transducer and activator of the transcription (STAT) pathway (Fig. 80.5). Decreased density of GH receptors in target organs may also play a role in GH resistance in children with CKD as suggested by reduced circulating levels of GH–binding protein (GHBP), a product of proteolytic cleavage of the GH receptor, which is decreased proportionally to the severity of renal dysfunction.

With CKD, IGF-1 resistance is also exacerbated by increased levels of circulating insulin-like growth factor binding proteins (IGFBPs) 1, 2, 4, and 6, which accumulate due to decreased renal clearance; these elevated IGFBPs that reduce bioavailable free IGF-1. Increased proteolysis of IGFBP 3, the major IGFBP that occurs in CKD, also decreases free IGF-1 available for the formation of IGF 1–ALS–IGFBP 3 complexes. The sum of these abnormalities results in impaired GH and IGF-1 effects on bone and altered growth in children with CKD.

The gonadotropic hormone axis is also altered in adolescent patients with CKD. Decreased renal clearance of gonadotropins leads to elevated serum gonadotropin levels and reduced pituitary secretion of bioactive luteinizing hormone. In uremia, increased serum levels of sex hormone-binding globulins significantly lower available free testosterone. Total testosterone levels are also reduced in these children. Moreover, serum testosterone is not positively correlated with the rate of GH secretion, as is the case in healthy children; in fact, GH secretion rates are lower than expected at each level of testosterone in boys with CKD. These physiologic abnormalities also contribute to pubertal growth impairment in adolescents with CKD.



• **Fig. 80.4** The GH–IGF-1 axis in normal children and children with chronic kidney disease. *ALS*, acid labile subunit; *GFR*, glomerular filtration rate; *GH*, growth hormone; *GHRH*, growth hormone releasing hormone; *IGF-1*, insulin like growth factor 1; *IGFBP*, insulin like growth factor binding protein; *SIRF*, somatostatin.



• **Fig. 80.5** GH-mediated Janus kinase/signal transducer and activator of the transcription signal transduction. *ALS*, acid labile subunit; *CIS*, cytokine-inducible SH2 protein; *GH*, growth hormone; *GHR*, growth hormone receptor; *IGF*, insulin-like growth factor; *JAK-2*, Janus kinase 2; *SOCS*, suppressors of cytokine signaling; *STAT*, signal transducer and activator of transcription.

Children with CKD may experience unrelated endocrinopathies, such as hypothyroidism or GH deficiency. This is important in evaluating a child with CKD and poor growth to exclude these disorders by determining thyroid levels, serum IGF-1, and bone age. If abnormalities are detected, referral to pediatric endocrinology is indicated.

Treatment

General Measures

In infants and young children with CKD, the most important measure to avoid growth failure is to provide adequate energy and protein intake. The importance of providing appropriate nutrition cannot be overstated. Without adequate nutrition, all other interventions to boost growth, such as rhGH therapy or vitamin D analogs, will prove ineffective. In general, initial target energy intake for children with CKD 2-4 and those on maintenance dialysis (MD) should be between 80% and 100% of the recommended daily allowance (RDA) for healthy children. Provision of adequate energy for growth may require nutritional supplements and supplementary feeding through a nasogastric tube or gastrostomy. Children treated with maintenance hemodialysis (HD) should have initial dietary protein intake based on RDA for chronologic age and an additional increment of 0.4 g/kg/day to account for extra dialysis losses. Children treated with maintenance peritoneal dialysis (PD) should have initial dietary protein intake based on RDA for chronologic age plus an additional increment of protein intake based on anticipated peritoneal losses, which vary greatly related to body size, peritoneal surface, and dialysis prescription.

The beneficial effect of correction of acidosis on growth retardation was initially described in children with renal tubular acidosis and normal renal function. Growth is better in CKD children with serum bicarbonate >22 mmol/L, and therefore it is recommended that serum bicarbonate be maintained >22 mmol/L in all children with CKD. In children on HD, the use of high sodium bicarbonate concentrations in dialysate as well as oral administration of sodium citrate or sodium bicarbonate should be individualized to maintain desired steady-state serum bicarbonate levels.

Providing adequate water and electrolyte replacements to replace excessive losses is essential to allow good growth in children with polyuria and/or salt-losing nephropathies. Unrelated endocrinopathies, such as hypothyroidism and GH deficiency, require specific interventions to promote good growth.

Dialysis and Intensified Dialysis

Although dialysis can improve the uremic state, longitudinal growth is usually not improved with standard conventional dialysis treatments alone. At a minimum, appropriate optimization of dialysis should be provided to promote growth. Unfortunately, in children and adolescents, long-term conventional PD or HD is linked with gradual loss of standardized height. Several large studies have documented mean annual losses of 0.2–0.8 SDS height in such children. Catch-up growth is not commonly observed in children on conventional HD or PD. Residual renal function is a more important predictor of growth on PD than standard dialytic clearance.

Catch-up growth may be enhanced using intensified dialysis protocols, either short daily or extended thrice-weekly sessions. Fischbach described improved growth when intensified HD (3 hours, 6 days per week) treatments were combined with rhGH. This approach delivered an average increase in growth velocity from 3.8 cm/year at baseline to 8.9 cm/year during the intervention. The benefit of intensified HD may result from improved clearance of uremic toxins. This additional clearance may also better address malnutrition–inflammation and metabolic acidosis, and it was associated with improved appetite and better growth in these children. There is also some evidence that use of biocompatible peritoneal dialysate is associated with better growth in children on PD for reasons that are not well understood.

Transplant

Only successful kidney transplantation is able to restore the conditions for normal growth compromised by the uremic state. However, growth rates after transplantation vary widely, with some recipients demonstrating further deterioration of standardized height while some, particularly younger children, experience catch-up growth. In a NAPRTCS analysis, the overall mean effect of transplantation performed before puberty on final adult height was no change in height SDS, confirming that the relative height achieved *at the time of transplantation* is the most important predictor of final adult height. Whereas pubertal children tend to lose standardized height scores following transplantation, good potential for posttransplant catch-up growth exists in children younger than 6 years. Infant allograft recipients typically exhibit the best posttransplant growth rates, demonstrating relative mean height gain of $+1.5$ SD within the first 2–7 years following transplant. Despite more widespread adoption of minimal steroid and steroid withdrawal protocols, catch-up growth in pubertal children continues to lag behind that seen in prepubertal children. A recent study of 389 German children posttransplantation demonstrated that, despite improved growth in many of these children after transplant in this era of less steroid therapy and rejection episodes, mean height of the recipients on average 4 years after transplantation was still low at -1.74 SDS, despite more efforts at steroid minimization.

Growth Hormone Therapy

Treatment of growth failure in children with CKD must be based on a thorough evaluation and therapy directed toward modifiable factors associated with growth impairment in the specific child. Recombinant GH (rhGH) therapy should be considered for any child with CKD 2–5 experiencing poor linear growth after correction of modifiable factors that may adversely affect growth. In these children, exogenous rhGH

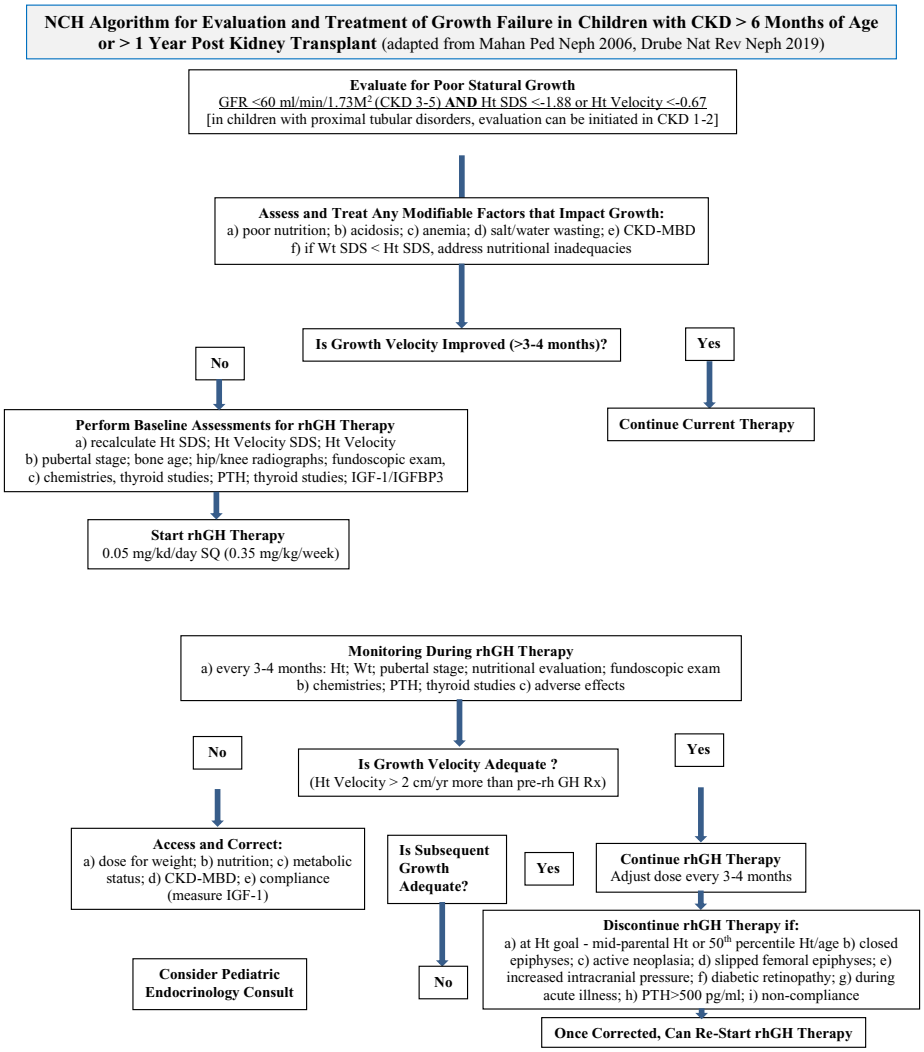
is able to overcome the effects of GH and IGF-1 resistance. In addition to promoting growth, rhGH therapy provides other benefits to children with CKD. GH treatment-related anabolic effects include improvements in body weight, mid-arm circumference, improved bone mineral density, and better lipid profiles. Table 80.2 lists additional benefits of rhGH in children with growth failure and CKD.

The algorithm in Fig. 80.6 for the evaluation and treatment of growth failure in children with CKD summarizes a logical stepwise approach to rhGH therapy in children with CKD. Before embarking on rhGH therapy, it is essential that all modifiable factors that may be hindering growth are addressed, particularly nutrition if the weight SDS is < height SDS (indicating inadequate calories for growth needs). Once metabolic and nutritional factors affecting growth have been properly addressed over a 3- to 6-month period, children who have not established normal growth velocity or achieved

TABLE 80.2 Rationale for the Use of rhGH in Children With CKD and Growth Failure

Improvement in linear growth and final adult height
Increased muscle mass and bone density
Better physical and social functioning
Improvement in psychosocial development
Decrease in overall morbidity and mortality
Decrease in hospitalizations
Reduced number of school days missed
Improved perception in overall health-related quality of life

CKD, Chronic kidney disease; *rhGH*, recombinant human growth hormone.



• **Fig. 80.6** Nationwide Children's Hospital (NCH) algorithm for evaluation and treatment of growth failure in children with chronic kidney disease. *CKD*, Chronic kidney disease; *GFR*, glomerular filtration rate; *GH*, growth hormone; *OFC*, occipital frontal circumference; *PTH*, parathyroid hormone; *SDS*, standard deviation score.

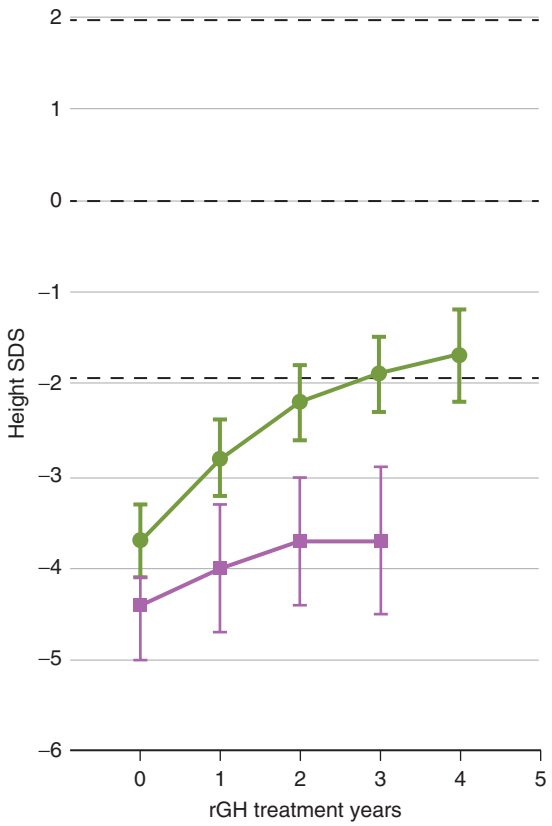
normal height for age should be evaluated for rhGH therapy. Height SDS, height velocity SDS, absolute height velocity, pubertal stage, and bone age should be assessed before treatment to confirm patient eligibility and provide baseline determinations for monitoring growth while receiving rhGH therapy. Baseline hip and knee x-rays, funduscopic examination, blood chemistries, parathyroid hormone (PTH) levels, and thyroid studies should be performed prior to treatment initiation. At baseline, IGF-1/IGFBP levels should be determined to serve as a baseline for assessing treatment response, if necessary. Once on rhGH therapy, ongoing monitoring for adverse events should be performed.

Following comprehensive pretreatment evaluation, children with no other cause for poor growth may be started on rhGH at 0.05 mg/kg/day (0.35 mg/kg/week or 28 IU/m^2/week) administered by subcutaneous injection. GH stimulation tests are not needed for children with CKD who experience poor growth after proper treatment of all modifiable factors that can affect growth. Throughout rhGH therapy, children must be monitored regularly (typically every 3–4 months) for dose modification based on weight gain, growth response to therapy, adverse events, and complicating factors that may further affect growth. There are no established studies that demonstrate better results with higher rhGH doses, but sometimes higher doses are tried in adolescents during puberty (up to 0.7 mg/kg/week) to attempt to achieve better height velocity and improvement in final adult height before epiphyses close.

Because rhGH administration increases plasma IGF-1 levels, and many of the growth-promoting effects of GH are mediated by IGF-1, it has been suggested that a relationship might exist between plasma IGF-1 concentrations and catch-up growth in children with rhGH therapy. In children with CKD receiving rhGH, serum IGF-1 may be a useful measure of therapeutic efficacy and adherence to therapy. Recombinant GH therapy should be discontinued when epiphyses close or if the child's height goal has been achieved (based on midparental height or 50th percentile height for age). Recombinant GH should be temporarily discontinued in the presence of active neoplasia, slipped capital femoral epiphyses, benign intracranial hypertension, diabetic nephropathy, during acute illness, severe hyperparathyroidism (PTH > 500 pg/mL), nonadherence with treatment, or at time of kidney transplantation. Close monitoring of growth should continue after discontinuing rhGH therapy because re-initiation of rhGH may be appropriate if height velocity decreases and reasons for the discontinuation of rhGH are resolved. In children who stop rhGH therapy due to complications, the majority demonstrate reduced growth velocity that improves if rhGH therapy can be restarted. Some children with genetic syndromes or neurologic disorders do not respond well to appropriate rhGH therapy, despite good nutrition and metabolic control, perhaps due to intrinsic somatic limitations.

Patients with CKD may experience alterations in both timing and duration of the normal pubertal growth spurt compared with healthy children. Multiple clinical studies in growth-retarded prepubertal children with CKD before dialysis have shown that treatment with rhGH increases height velocity during the first treatment year almost twofold compared with baseline or placebo-treated children. No acceleration in bone maturation was observed in these studies; therefore, predicted adult height steadily increased during treatment with rhGH. Additional studies have shown that the response to rhGH is significantly less in dialyzed children compared to children with earlier CKD, as shown in Fig. 80.7. In addition, the cumulative height gained during treatment with rhGH was positively affected by the duration of therapy as well as the initial target height deficit and negatively affected by the duration of dialysis.

In children who receive sufficient rhGH therapy prior to dialysis, the relative height gain attained during rhGH therapy with rhGH appears to be maintained, even after kidney transplantation, so that final adult height in the normal range is typically achieved. For contrast, in Hokken-Koelega's retrospective study of 52 children who underwent kidney transplantation before the age of 15 years, those with short stature who did not receive rhGH therapy at the time of the first dialysis experienced further height SDS decrease during dialysis, and their height SDS did improve following kidney transplantation. The final adult height of



• **Fig. 80.7** Superior efficacy of growth hormone treatment in children with chronic kidney disease stages 2–4 (*n* = 19, *circles*) versus dialysis (*n* = 6). *rGH*, recombinant growth hormone; *SDS*, standard deviation score.

these patients remained below the third percentile for age for 77% of the males and 71% of the females.

In the largest study to address side effects with rhGH therapy in children with CKD, Fine and colleagues compared the frequency of rhGH-related adverse events in patients in the NAPRTCS registry to untreated children with CKD. Compared with untreated children, rhGH-treated patients showed no significant increase in the incidence of malignancy, slipped capital femoral epiphysis, avascular necrosis, acceleration of bone maturation, deterioration of renal function, or acute allograft rejection.

Summary

Growth failure remains a significant clinical problem in children with CKD and has been linked to both adverse medical and psychological outcomes. Growth failure in this population is usually multifactorial; it may reflect substantial derangements of the GH–IGF-1 axis and may be compounded by nutritional and metabolic abnormalities, each of which must be adequately addressed to improve growth. The safety and efficacy of rhGH therapy in growth-impaired children with CKD have been demonstrated in numerous clinical trials. Growth response to therapy with rhGH is positively associated with residual renal function and duration of treatment. The milder the initial height deficit at initiation of rhGH therapy, the better chances of reaching final adult height in the normal range. The benefits of improved growth impact children with CKD in childhood and continue to provide positive social and health benefits.

Recommended Reading

Akchurin OM, et al. Approach to growth hormone therapy in children with chronic kidney disease varies across North America: the Midwest Pediatric Nephrology Consortium report. *BMC Nephrol.* 2017;18(1):181. https://doi.org/10.1186/s12882-017-0599-1.

The variability in how pediatric nephrologists introduce and monitor GH therapy in children with CKD was highlighted in this large survey study.

Al-Uzri A, et al. The impact of short stature on health-related quality of life in children with chronic kidney disease. *J Pediatr.* 2013;163(3):736–741 e1.

This analysis from the Chronic Kidney Disease in Childhood (CKiD) study found that height gains and GH use were associated with increases in physical and social functioning by parent quality-of-life reports.

Bamgbola FO, Kaskel FJ. Uremic malnutrition-inflammation syndrome in chronic renal disease: a pathobiologic entity. *J Ren Nutr.* 2003;13(4):250–258.

This analysis of the role of malnutrition and inflammation on growth and other outcomes in children with CKD was an important early work in this field.

Belgorosky A, et al. Serum sex hormone-binding globulin and serum nonsex hormone-binding globulin-bound testosterone fractions in prepubertal boys with chronic renal failure. *J Clin Endocrinol Metab.* 1991;73(1):107–110.

This early report defined the abnormalities of testosterone and binding proteins in young boys with CKD.

Boehm M, et al. Early erythropoietin therapy is associated with improved growth in children with chronic kidney disease. *Pediatr Nephrol.* 2007;22(8):1189–1193.

This registry study demonstrated the association of better growth with higher hemoglobin and erythropoietin therapy in children with CKD.

Boirie Y, et al. Alterations of protein metabolism by metabolic acidosis in children with chronic renal failure. *Kidney Int.* 2000;58(1):236–241.

This report defined abnormalities in protein metabolism induced by metabolic acidosis in a small group of carefully studied young children with CKD.

Broyer M, et al. Long-term social outcome of children after kidney transplantation. *Transplantation.* 2004;77(7):1033–1037.

This French observational cohort study presented encouraging results about adult social outcomes and underscores the importance of children who receive a renal transplant reaching normal adult height in these outcomes.

Camargo MF, et al. Growth of children with end-stage renal disease undergoing daily hemodialysis. *Pediatr Nephrol.* 2014;29(3):439–444.

This prospective observational study conducted in a single Brazilian center demonstrated the beneficial growth-promoting effects of daily hemodialysis, especially in small children.

Drube J, et al. on behalf of the European Society for Paediatric Nephrology Chronic Kidney Disease Mineral and Bone Disorders, Dialysis, and Transplantation Working Groups. Clinical practice recommendations for growth hormone treatment in children with chronic kidney disease. *Nat Rev Nephrol.* 2019;15:577–589.

This premier evidence-based presentation of best clinical practice guidelines for GH treatment of children with CKD was developed by a European multinational group of 12 experts in pediatric kidney disease.

Fine RN, Ho M, Tejni A, Blethen S. Adverse events with rhGH treatment of patients with chronic renal insufficiency and end stage renal disease. *J Pediatr.* 2003;142:539–545.

This important report from NAPRTCS on adverse events with rhGH compared children treated with rhGH to large population of similar children not treated with rhGH to demonstrate no significant differences in adverse events between groups (except intracranial hypertension [ICH], although of the three rhGH patients with ICH, two had it occur only after discontinuation of rhGH).

Fine RN. Etiology and treatment of growth retardation in children with chronic kidney disease and end-stage renal disease: a historical perspective. *Pediatr Nephrol.* 2010;25(4):725–732.

This interesting commentary provided valuable insights on our increasing understanding of the causes and effective interventions for growth failure in children with CKD.

Fine RN, Martz K, Stablein D. What have 20 years of data from the North American Pediatric Renal Transplant Cooperative Study taught us about growth following renal transplantation in infants, children, and adolescents with end-stage renal disease? *Pediatr Nephrol.* 2010;25(4):739–746.

A fascinating exploration of new insights and conclusions about growth in children with CKD derived from the body of studies contributed by NAPRTCS reviewed by one of the leaders in the field.

Fischbach M, et al. Daily online haemodiafiltration promotes catch-up growth in children on chronic dialysis. *Nephrol Dial Transplant.* 2010;25(3):867–873.

The beneficial impact of daily hemodiafiltration on growth in children was documented in this prospective observational cohort single-center study from France.

Franke D, et al. Patterns of growth after kidney transplantation among children with ESRD. *Clin J Am Soc Nephrol.* 2015;10(1):127–134.

This paper reported the growth outcomes of children followed in the German CKD Growth and Development Study and describes the benefits of reduced corticosteroid exposure and optimal metabolic control before and after transplantation in this population.

Furth SL, et al. Growth failure, risk of hospitalization and death for children with end-stage renal disease. *Pediatr Nephrol.* 2002;17(6):450–455.

This U.S. Renal Data System study was the first to detail the increased rates of hospitalization and death in children with ESKD who are short compared to normal-height children with ESKD.

Haffner D, Nissel R. Growth and puberty in chronic kidney disease. In: Geary D, Schaefer F, eds., Comprehensive Pediatric Nephrology. Philadelphia: Mosby Elsevier; 2008:694–717.

This chapter provided a detailed review of the important information regarding growth and puberty in children with CKD.

Harambat J, et al. Adult height in patients with advanced CKD requiring renal replacement therapy during childhood. *Clin J Am Nephrol.* 2014;9:92–99.

This detailed review of potential determinants of final adult height in CKD was derived from a large cohort of 1612 patients from 20 European countries who started renal replacement therapy before 19 years of age.

Hokken-Koelega AC, et al. Growth after renal transplantation in prepubertal children: impact of various treatment modalities. *Pediatr Res.* 1994;35(3):367–371.

This multicenter Dutch observational study of growth in children after renal transplantation demonstrated the deleterious effects of impaired renal function and corticosteroid cumulative dose on growth in these children.

Hokken-Koelega AC, et al. Growth hormone treatment in growth-retarded adolescents after renal transplant. *Lancet.* 1994;343(8909):1313–1317.

This Dutch observational study represented one of the best demonstrations of the safety and efficacy of GH therapy in children after renal transplantation.

Ingulli EG, Mak RH. Growth in children with chronic kidney disease: role of nutrition, growth hormone, dialysis, and steroids. *Curr Opin Pediatr.* 2014;26(2):187–192.

The authors presented an excellent review of the interplay of nutrition and other factors on growth in children with CKD.

Janjua HS, Mahan JD. Growth in chronic kidney disease. *Adv Chronic Kidney Dis.* 2011;18(5):324–331.

This review detailed the factors responsible for growth delay and effects of interventions to promote growth in children with CKD.

Kaskel F. Chronic renal disease: a growing problem. *Kidney Int.* 2003;64(3):1141–1151.

This presented a useful review of the factors that lead to poor growth in children with CKD and available interventions.

Ketteler M, et al. Executive summary of the 2017 KDIGO chronic kidney disease–mineral and bone disorder (CKD-MBD) guideline update. *Kidney Int.* 2017;92:26–36.

This provided a very useful summary of the most important differences and improvements in the 2017 KDIGO CKD-MBD guidelines and some perspectives on the likely value of these enhancements.

Mahan JD, Warady BA. Assessment and treatment of short stature in pediatric patients with chronic kidney disease: a consensus statement. *Pediatr Nephrol.* 2006;21(7):917–930.

This consensus statement aptly summarized the state of knowledge and evidence on issues related to growth and GH treatment in children with CKD and provided an evaluation and treatment algorithm that is still most useful today.

Maniar S, et al. Growth hormone action is blunted by acidosis in experimental uremia or acid load. *Clin Nephrol.* 1996;46(1):72–76.

This experimental study demonstrated the inhibitory effects of acidosis on the growth response to GH despite increases in protein syntheses in uremic rats.

McSherry E, Morris Jr RC. Attainment and maintenance of normal stature with alkali therapy in infants and children with classic renal tubular acidosis. *J Clin Invest.* 1978;61(2):509–527.

The classic paper demonstrated the beneficial growth-promoting effects of alkali therapy in children with renal tubular acidosis.

National Kidney Foundation. KDOQI clinical practice guideline for nutrition in children with CKD: 2008 update. *Am J Kidney Dis.* 2009;53(suppl 2):S1–S124.

This paper summarized the evidence-based recommendations from the National Kidney Foundation for nutrition and other therapies to best promote growth in children with CKD.

Neu AM, et al. Growth in adolescent hemodialysis patients: data from the Centers for Medicare & Medicaid Services ESRD Clinical Performance Measures Project. *Pediatr Nephrol.* 2005;20(8):1156–1160.

Adolescents in the Centers for Medicare and Medicaid Services database were analyzed to demonstrate their poor linear growth and worsening height standard deviation scores despite the dialysis intervention.

Nissel R, et al. Effect of renal transplantation in childhood on longitudinal growth and adult height. *Kidney Int.* 2004;66(2):792–800.

This retrospective study from a single center in Germany demonstrated that children who receive a renal transplant in childhood experience moderate catch-up growth before puberty, but that final adult height is reduced in about one-third as a result of reduced pubertal height gain and preexisting height deficits at renal transplantation.

North American Pediatric Renal Trials and Collaborative Studies 2011 annual report. http://www.NAPRTCS.org.

This report from the premier North American registry and collaborative research organization devoted to children with CKD and kidney transplants provided detailed evidence about the care and outcomes of these children.

Rees L. Growth hormone therapy in children with chronic kidney disease after more than two decades of practice. *Pediatr Nephrol.* 2016;31:1421–1435.

This outstanding review integrated the extensive experience of with the evaluation and management of growth in children with CKD at Great Ormond Street, UK, with the latest evidence on this topic from the literature and from Cochrane reviews.

Rodig NM, et al. Growth in children with chronic kidney disease: a report from the Chronic Kidney Disease in Children Study. *Pediatr Nephrol.* 2014;29(10):1987–1995.

This CKiD registry analysis reported continued suboptimal growth outcomes and opportunities for better control of alkalosis and GH therapy in children with CKD.

Rosenkranz J, et al. Psychosocial rehabilitation and satisfaction with life in adults with childhood onset of end-stage renal disease. *Pediatr Nephrol.* 2005;20(9):1288–1294.

This detailed single German center study of quality of life and vocational rehabilitation in adults who underwent kidney transplantation as a child demonstrated their general and health-related satisfaction was significantly reduced compared to the general population and in proportion to their adult height.

Salevic P, et al. Growth in children with chronic kidney disease: 13 years follow up study. *J Nephrol.* 2014;27(5):537–544.

The authors described growth in children from the Serbian Pediatric Registry of Chronic Kidney Disease and demonstrate inferior outcomes for those with hereditary renal disease and those who require dialysis and positive outcomes for those who receive a kidney transplant.

Schaefer F, Mehls O. Endocrine, metabolic and growth disorders. In: Barrat T, Holliday MA, Avner ED, eds. *Pediatric Nephrology.* Baltimore: Williams & Wilkins; 1994:1241–1286.

This chapter presented the early original research that defined the interplay of endocrine, metabolic, and nutritional factors that affect growth in children with CKD.

Schaefer F, et al. Alterations in growth hormone secretion and clearance in peripubertal boys with chronic renal failure and after renal transplantation. Cooperative Study Group of Pubertal development in Chronic Renal Failure. *J Clin Endocrinol Metab.* 1994;78(6):1298–1306.

An elegant study that used deconvolution analysis defined the negative impact of both uremia and corticosteroids on GH secretion in peripubertal boys with CKD and post renal transplantation.

Shroff R, et al. Effects of hemodiafiltration versus conventional hemodialysis in children with ESKD: the HDF, hear and height study. *J Am Soc Nephrol.* 2019;30:678–691.

Detailed follow-up of one year of 190 children maintained on hemodiafiltration (HDF) or hemodialysis that demonstrated superior cardiovascular and growth outcomes in the HDF group. The authors correctly advocate for a true randomized trial to confirm these observations.

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Adequacy of Peritoneal Dialysis/Assessing Peritoneal Function in Pediatric Patients

VIMAL CHADHA, MD • BRADLEY A. WARADY, MD

End-stage kidney disease (ESKD) is a debilitating disease, and its consequences are particularly detrimental in children who face a lifelong treatment burden. In the absence of the availability of a preemptive kidney transplant, dialysis initiation in children is recommended at an estimated glomerular filtration rate (eGFR) of < 10 mL/min/1.73 m^2 or at a greater eGFR level when the patient's clinical course is complicated by the presence of malnutrition, fluid overload, hypertension, hyperkalemia, hyperphosphatemia, acidosis, growth failure, or neurological consequences of uremia and these symptoms are refractory to medication and or dietary management. While the provision of dialysis is an integral component of comprehensive ESKD management, it is apparent that to achieve the best possible outcome, optimal management of all the ESKD-related comorbidities is equally important and is rightly considered by most as pertinent components of the dialysis care of children, in addition to the solute and fluid removal accomplished by dialysis. It is worth noting that while the therapeutic endpoints of many of these clinical issues are relatively well defined, there is no consensus on what constitutes "adequate dialysis" in terms of solute clearance.

In adults, dialysis adequacy has conventionally been characterized by urea removal (small solute clearance) with specific quantitative targets based on evidence of an association between solute clearance and patient morbidity/mortality. This association has been clearer in the hemodialysis (HD) population in contrast to the experience of adults who receive peritoneal dialysis (PD). Similar outcome parameters are difficult to apply to children because of the low mortality rate experienced by patients in this age group and the absence of any well-substantiated correlations between their clinical status and the small solute clearance achieved by dialysis. Furthermore, the provision of evidence-based pediatric PD adequacy guidelines is hampered by a crucial epidemiologic issue, because ESKD remains a relatively uncommon disease in children and a significant proportion of patients receive a kidney transplant soon after developing ESKD, there is limited long-term pediatric dialysis outcome data and thus an inability to detect an effect of the delivered PD dose on pediatric patient outcomes. Accordingly, more than a decade ago, the pediatric component of the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) PD adequacy guidelines suggested that the clinical "wellness" of the individual patient should remain an important treatment goal and an important means by which the adequacy of care should be measured.

The recent International Society for Peritoneal Dialysis (ISPD) practice recommendations emphasize that the well-being of the person receiving dialysis, both child and adult, is related to many different factors and not just the removal of specific toxins. Accordingly, the focus of the dialysis prescription has shifted from simply achieving "an adequate Kt/V_{urea}" to delivering "high-quality, goal-directed" dialysis care. The treatment goals should be realistic and established through shared decision making between the care team and the patient (and/or care provider for young children) with the aims to (1) maintain quality of life (QOL) for the person receiving PD as much as possible by enabling them to meet their life goals, (2) minimize symptoms of associated CKD comorbidities and treatment burden while (3) ensuring the provision of high-quality dialysis care by the dialysis team.

This goal-directed approach concurs with the findings from the Standardized Outcomes in Nephrology–PD initiative (https://songinitiative.org/projects/song-pd/), which identified core outcomes for PD chosen by patients, caregivers, and health care professionals. While retaining the basic concepts of dialysis adequacy and key issues from the KDOQI 2006 guidelines in this chapter, we have included the latest ISPD recommendations with an emphasis on the provision of goal-directed dialysis delivery.

Dialysis Adequacy in Terms of Small Solute Clearance (Kt/V_{urea})

The concept of adequate dialysis was born over 40 years ago when a systematic analysis of the National Cooperative Dialysis Study (NCDS) involving adult HD patients revealed that the relationship between dialysis dose and patient outcome was not linear, and increasing the dialysis dose beyond a certain threshold did not result in any additional beneficial outcomes. A number of publications by the Dialysis Outcomes and Practice Patterns Study (DOPPS) over the last two decades have supported the observation that for adult patients who receive a standard thrice-weekly course of dialysis, a $Kt/V_{urea} < 1.2$ per session is associated with increased mortality; however, a $Kt/V_{urea} > 1.3$ has not been shown to be consistently associated with a survival benefit.

Because of initial enthusiasm with the assessment of small solute clearance in patients receiving HD, the concept of Kt/V_{urea} (but on a weekly basis) was extrapolated for use in PD patients despite obvious differences between the two therapies. In contrast to the intermittent nature of HD, PD is a continuous treatment, and while it provides lower rates of small solute clearance per unit time, it provides similar survival rates compared to HD. This survival benefit with PD is assumed to be because of the more effective removal of "middle molecules" (those with molecular weight between 500 and 5000 kDa) associated with the therapy; it is speculated that the improved middle molecule clearance seen in patients receiving PD might be because of greater preservation of residual kidney function (RKF) in PD as compared to HD (and thus better urinary middle molecule clearance) rather than effects of PD membrane permselectivity itself. The substantial impact of preserved RKF has previously been supported by a reanalysis of the CANUSA study of adult continuous ambulatory PD (CAPD) patients and the adult ADEMEX study.

In terms of solute clearance, the ADEMEX trial, in which patients were randomized to standard versus enhanced PD prescriptions, demonstrated that there was no survival benefit associated with a Kt/V_{urea} of > 1.7/week, and RKF was the most important factor influencing survival rates. Observational studies in adult PD patients without RKF have shown decreased survival with a lower Kt/V_{urea}. Lo et al. reviewed data from 150 anuric PD patients over a 10-year period and suggested a minimal peritoneal Kt/V_{urea} target of 1.7 and an optimal target of 1.8 in anuric patients. On the basis of ADEMEX and the study of Lo et al., the KDOQI 2006 PD Adequacy guidelines recommended a Kt/V_{urea} target of 1.7 per week for adult patients. As will be discussed later, the Kt/V_{urea} target for children was somewhat empirically determined to be slightly greater than the adult value. Although the importance of Kt/V_{urea} in PD has arguably been losing emphasis, its use is still recommended to help gauge the adequacy of dialysis in the absence of any other simplified quantitative measure.

Thus, an adequate dose of PD has best been defined as the minimum dose, in terms of the quantity of solute removed, below which a clinically unacceptable rate of negative outcomes occur. In contrast, the optimal dose of dialysis is that dose above which no significant reduction in negative outcomes or improvement in positive outcomes occur to justify the additional patient burden or cost; it lies somewhere between the minimal effective (adequate) dose and the maximal dose, or the dose above which there are clearly no additional benefits. However, as noted earlier, it is difficult to define the optimal PD dose in children with confidence because of the absence of definitive data correlating dialysis dose to patient outcome. Thus the recommended clinical practice is, in essence, to provide the most dialysis that can be delivered to the pediatric patient within the constraints of social and clinical circumstances, QOL, and cost, taking into account the local country resources.

The provision of adequate dialysis must therefore target an individualized goal-directed prescription based on the desired volume removal (ultrafiltration [UF]) and solute clearance required to maintain optimal fluid balance and achieve nutritional/metabolic goals, in addition to meeting the psychosocial and financial needs of the child and their family.

Prescription of Peritoneal Dialysis

Choice of Peritoneal Dialysis Modality

Both CAPD and automated PD (APD) are used by children, although the latter is the preferred PD modality where resources allow, in large part because its use is characterized by freedom from dialysis procedures during daytime hours. The provision of an APD cycling device is associated with an increased cost and a slight increase in complexity relative to CAPD. APD has classically been divided into APD with a day-dwell, also known as continuous-cycling PD (CCPD), and dry-day APD, also known as nocturnal intermittent PD (NIPD).

An alternative form of APD is tidal PD (TPD), in which the patient is provided with an initial fill volume followed by partial drainage at periodic intervals. Initially, the principal purpose of TPD was to enhance clearance of small solutes; however, it is primarily used now to serve as a treatment for the "drain pain" that occurs in some patients during drainage of dialysate from the peritoneal cavity. Largely, as a result of its complexity and high cost, TPD is not widely used. Finally, adapted APD (aAPD) is another modified PD prescription that uses varied dwell times and fill volumes in an effort to improve small solute clearance, UF, and sodium removal.

As both CAPD and APD modalities can provide adequate small solute clearances, the former is often used effectively in developing countries because of substantial cost savings. In wealthier countries, the use of APD predominates in infants, children, and adolescents. Nonetheless,

final selection of the dialysis modality should also take into account the patient/parents/caregivers' choice, the child's age and size, presence of comorbidities, available family support, local resources, and expertise of the dialysis team.

Initial Dialysis Prescription

The initial prescription should take into account the patient's body surface area (BSA), exchange dwell time, the RKF, and the desired fluid removal. In view of the age-independent relationship between peritoneal surface area and BSA, the use of BSA as a scaling factor for the prescribed fill volume is recommended. Whereas the target range for the fill volume of patients greater than 2 years of age is 1000–1200 mL/m^2 BSA, the initial prescribed volume should be somewhat lower for smaller infants (600–800 mL/m^2 BSA) and the fill volume should be increased in a stepwise manner, as tolerated by the patient. To optimize small-solute clearance, minimize cost, and possibly decrease the frequency of exchanges, one should first increase the instilled volume per exchange (maximum 1400 mL/m^2 BSA) as tolerated by the patient before increasing the number of exchanges per day. The volume of the supine exchange(s) should be increased first, as this is the position with the lowest intra-abdominal pressure. Objective evidence of patient tolerance may require measurement of the intraperitoneal pressure.

The PD prescription process should also take into consideration the peritoneal membrane transport characteristics as defined by the peritoneal equilibration test (PET) (vide infra), which helps define the optimal frequency of exchanges and the dialysate dextrose concentration (1.5%, 2.5%, or 4.25%) required (along with RKF, if it exists) to achieve the targeted solute and fluid removal. It should be recognized that it is often impractical to consider the provision of a dialysis prescription solely based on kinetic data and achieved solute clearance without reference to social constraints such as school attendance and the working schedule of parents.

Patients receiving APD usually remain on the cycler for 8–10 hours during the nighttime and maintain a daytime fill volume that is typically one-half the nocturnal fill volume. The use of NIPD, characterized by the absence of any daytime dwell, can be considered in pediatric patients who are clinically well, whose combined dialysis prescription and RKF achieves or exceeds the target solute clearance, and who are without evidence of hyperphosphatemia, hyperkalemia, hypervolemia, or acidosis. Patients who do not meet these criteria and receive cycler dialysis are generally prescribed CCPD.

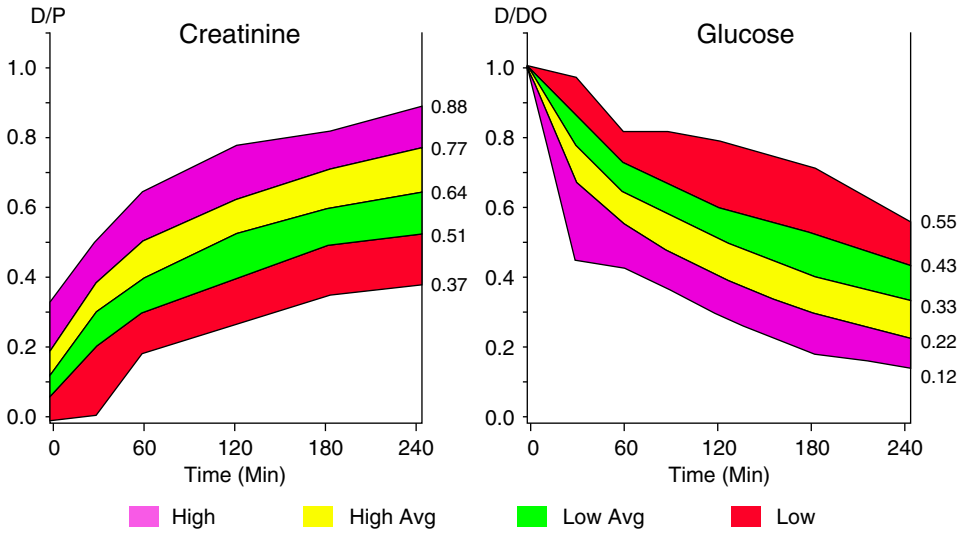
Patients receiving CAPD perform three to five daily exchanges using a double-bag PD solution with a Y-set disconnectable system. Drainage of spent dialysate and inflow of fresh dialysis solution are performed manually, relying on gravity to move fluid into and out of the abdomen. When there is inadequate UF overnight because of rapid glucose absorption, especially when the peritoneal membrane transport capacity is high, a higher dextrose concentration or an icodextrin-based PD solution can be employed for the prolonged nighttime exchange.

The presence of RKF at the start of PD may enable individuals to start on a low-dose prescription that may be incrementally increased as RKF declines or as clinically indicated. This may allow patients more time for life participation, less treatment burden, and a better QOL.

Peritoneal Equilibration Test

The PET was developed as a clinically applicable means of characterizing solute transport across the peritoneum and is the most common technique used in children to assess the peritoneal membrane transport capacity and guide the prescription process. The procedure yields data necessary to determine the fractional equilibration of creatinine and glucose between dialysate and blood expressed as the dialysate to plasma (D/P) ratio for creatinine and the ratio of dialysate glucose to initial dialysate glucose (D/D$_O$) (Fig. 81.1). The test fill volume should be 1000–1100 mL/m^2 when the procedure is conducted in children. The provision of a smaller volume, which is often necessary for young infants, may result in more rapid equilibration and the artifactual appearance of an inherently more rapid membrane transport capacity. Although the specific details of the PET are discussed in Chapter 20, it is important to highlight the fact that glucose in high concentration (as occurs in dialysis fluid) interferes with the measurement of creatinine by the photometric method. The resulting creatinine value is falsely elevated. Accordingly, the creatinine concentration in dialysis fluid should either be measured by the enzymatic assay method in which there is no glucose interference, or the creatinine values must be corrected for glucose interference by determining a correction factor for the individual laboratory.

It has been suggested that a patient's initial PET evaluation should be performed approximately 1 month after dialysis initiation to facilitate categorization of a patient's transport capacity in the most accurate manner. Patients are categorized as high, high average, low average, or low solute transporters based on a comparison of their data to reference norms. A child who is classified as a rapid transporter is likely to dialyze most efficiently in terms of solute and water removal by using short, frequent dialysis cycles as in APD. On the other hand, a low or low average transporter may benefit most from a schedule that includes longer dwell times as in classical CAPD. Attention to these prescription issues may be particularly important to children because of the high incidence of cardiac disease, the goal of achieving euvolemia, and normotension (vide infra). Whereas routine repetition of the PET evaluation is not indicated, repeat testing should be considered when there is clinical/biochemical evidence of suboptimal dialysis or when clinical events have occurred (e.g., repeated peritonitis) that may have altered the membrane transport capacity.



• **Fig. 81.1** Peritoneal transport characteristics of creatinine and glucose according to the standardized peritoneal equilibration test. *D/D*$_O$, dialysate glucose to initial dialysate glucose ratio; *D/P*, dialysate to plasma ratio. (Modified with permission from Warady BA, Alexander SR, Hossli S, et al. Peritoneal membrane transport function in children receiving long-term dialysis. *J Am Soc Nephrol*. 1996;7:2385-2391.)

Personal Dialysis Capacity Test

The personal dialysis capacity (PDC) test is based on the three-pore model of solute and fluid transport across the peritoneum. The PDC test describes the peritoneal membrane transport characteristics by functional parameters, which are calculated based on data obtained from several exchanges of different duration and performed with PD solutions of different glucose concentrations over a day. While validated in children, the prolonged duration of the test has negated its clinical application in most centers.

Mass Transfer Area Coefficient

The mass transfer area coefficient (MTAC) is an additional measure of solute transport capacity and is the most precise means of estimating intrinsic peritoneal membrane permeability to a specific solute. Unlike the D/P ratio determined with the PET, the MTAC is essentially independent of dialysis mechanics such as the fill volume and dialysate dextrose concentration. Normative pediatric MTAC data have been published.

Measurement of Peritoneal Dialysis Dose

As noted previously, a reproducible measure of the dose of PD is essential to determine the quantity of dialysis delivered to an individual patient. The total (RKF + dialysis) weekly Kt/V_{urea} and the total weekly creatinine clearance (C_{Cr}) are the best available measures of PD dose, and both have been used in clinical practice. The determination of dialysis and urine Kt/V_{urea} alone is recommended based on the simplicity of the calculation and the fact that studies in adult patients on PD have not provided any evidence of an additional benefit in terms of patient outcome when expressing clearance in any manner other than Kt/V_{urea}.

Kt/V_{urea} is a measure of the amount of plasma cleared of urea during the sampling period (K*t) normalized to total body water (TBW) or V, the volume of urea distribution. The total weekly Kt/V_{urea} is calculated as follows:

$$\text{Weekly } Kt/V = \frac{D_{ur} \times V_D + (U_{ur} \times V_u)}{P_{ur} \times V} \times 7$$

where D_{ur}, U_{ur}, and P_{ur} are the dialysate, urinary, and plasma concentrations of urea; V_D and V_U are the 24-hour dialysates and urine volumes, and V is the urea distribution volume.

In the calculation of Kt/V_{urea}, it is most important to use an accurate estimate of V. Traditionally, anthropometric prediction equations based on height and weight, such as those of Mellits and Cheek, have been used to estimate V. However, such equations were established in healthy populations, and subsequent studies have revealed that the use of these equations routinely overestimates V (or TBW) in pediatric patients receiving PD. In contrast, the determination of TBW by heavy water ($H_2^{18}O$ or D_2O) dilution in 64 pediatric patients receiving PD has allowed for the development of accurate TBW prediction equations. The gender-specific equations are as follows:

$$\text{Males}: TBW = 0.10 \times (\text{height} \times \text{weight})^{0.68} - (0.37 \times \text{weight})$$

$$\text{Females}: TBW = 0.14 \times (\text{height} \times \text{weight})^{0.64} - (0.35 \times \text{weight})$$

Gender-specific nomograms to estimate TBW that are based on these equations are available in the KDOQI PD Adequacy guidelines.

Because the height × weight parameter also predicts BSA, it has been possible to simplify the prediction equations by utilizing BSA as determined by the Gehan and George equation (vide infra). Although slightly less precise than the best-fitting equations, these equations might be considered more "user friendly":

$$\text{Males}: \text{TBW} = 20.88 \times \text{BSA} - 4.29$$
$$\text{Females}: \text{TBW} = 16.92 \times \text{BSA} - 1.81$$

In obese and malnourished patients, the TBW calculation should be based on the patient's ideal body weight to avoid overdialysis in the former and underdialysis in the latter group of patients.

As noted previously, the measurement of total small solute clearance also requires the determination of RKF and BSA. In addition to the positive impact of RKF on patient survival as demonstrated in studies of adult PD patients, the presence of RKF in children has been shown to be associated with improved height SDS. The RKF is calculated as the glomerular filtration rate (GFR) by determining the average of the clearance of urea and creatinine as follows:

$$\text{RKF} = \left[\frac{U_{cr} \times V_u}{P_{cr}} + \frac{U_{ur} \times V_u}{P_{ur}} \right] \Big/ 2$$

where U_{cr} and P_{cr} are urinary and plasma concentrations of creatinine, U_{ur} and P_{ur} are urinary and plasma concentrations of urea, and V_u is the 24-hour urine volume. This method mathematically balances the tubular secretion of creatinine and the tubular reabsorption of urea, which is characteristic of CKD. During the first few years of dialysis therapy, RKF often contributes appreciably to total solute and water removal. The loss of RKF is the major cause of a decreasing total (dialysate and RKF) clearance in PD subjects followed longitudinally and must be compensated by changes in the dialysis prescription to maintain the desired level of total clearance.

The determination of BSA has historically been derived using the method of DuBois and DuBois, and previously available data were based on this method. However, in an independent comparison, the Gehan and George method was preferred because more than 400 subjects, including many children, were used to define this formula; in contrast, only 9 subjects were used to define the formula of DuBois and DuBois. The respective formulae are as follows:

$$\text{DuBois and DuBois method}: \text{BSA}\left(\text{m}^2\right) = \left(71.84 \times \text{Wt}\left(\text{kg}\right)^{0.425} \times \text{Ht}\left(\text{cm}\right)^{0.725}\right) \Big/ 10{,}000$$
$$\text{Gehan and George method}: \text{BSA}\left(\text{m}^2\right) = 0.0235 \times \text{Wt}\left(\text{kg}\right)^{0.51456} \times \text{Ht}\left(\text{cm}\right)^{0.42246}$$

Adequacy Recommendations

As mentioned previously and as reflected by the recent ISPD recommendations, dialysis adequacy should encompass a more comprehensive assessment of patient well-being, including QOL and patient-specified goals, sufficient small solute and middle molecule clearance, optimal fluid management and blood pressure control, bone-mineral health with normal serum phosphorus in the context of minimizing mortality and morbidity, and a livable dialysis regimen for the patient. In the case of children, adequate growth, healthy nutritional status, and adequate psychomotor development are additional important parameters that should be included in the assessment of dialysis adequacy.

Solute Clearance

As noted previously, targeting Kt/V_{urea} remains a cultural fixation in ESKD care, despite evidence that urea removal does not reflect the clearance of all uremic toxins. Nonetheless, it provides a (relatively) reproducible measure that can guide clinicians and help to avoid grossly inadequate dialysis. In turn, it will likely remain important for regulatory and quality assurance purposes for the foreseeable future. The 2006 KDOQI PD Adequacy guidelines pertaining to children recommend achieving a total (peritoneal and RKF) Kt/V_{urea} of at least 1.8/week. Of course, in those without RKF, the Kt/V_{urea} of > 1.8 should be achieved by peritoneal clearance alone. In contrast, the newly published ISPD practice recommendations suggest that the PD prescription should be adjusted with the goal of achieving a normal serum phosphate level because of the important influence poor phosphorus control has on cardiovascular outcomes. In addition, a total minimum weekly Kt/V_{urea} of 1.7 should be targeted in children receiving PD, with modifications based on regular assessment of clinical well-being and laboratory parameters. It is noteworthy that neither set of guidelines set different targets for continuous and noncontinuous forms of PD such as NIPD, nor do they set different targets based on peritoneal transport status.

Emphasized in the ISPD practice recommendations is the recommendation that in the patient who is otherwise thriving, failure to achieve specific numeric targets (e.g., Kt/V_{urea}) may not be an indication to alter the dialysis prescription or modality. Alternatively, it is important to recognize that grossly inadequate solute clearance may occur in patients who show only subtle clinical signs of inadequate dialyses, such as a deteriorating nutritional state. Therefore, regardless of the delivered dose of dialysis, if a patient is not doing well and has no identifiable cause for the poor clinical status other than kidney failure, a trial of increased dialysis is indicated.

Clinical features that may be suggestive of inadequate dialysis and factors that may contribute to this outcome are listed in Tables 81.1 and 81.2, respectively.

TABLE 81.1 Outcome Measures That May Be Associated With Inadequate Dialysis

- Lack of subjective feeling of well-being
- Clinical or biochemical signs of malnutrition (e.g., low body mass index, low serum albumin)
- Poor growth/poor response to recombinant growth hormone
- Developmental delay
- Poor school performance
- Poor response to anemia management
- Poor control of renal osteodystrophy
- Excessive calcium × phosphorus product
- Uncontrolled hypertension
- Congestive heart failure

TABLE 81.2 Factors Contributing to Inadequate Dialysis

- Loss of residual kidney function
- Prescription inadequate for peritoneal membrane transport characteristics
- Reduced peritoneal surface area due to extensive intra-abdominal adhesions
- Loss of membrane solute transport/ultrafiltration capacity due to peritonitis
- Noncompliance with PD prescription
- Poorly functioning PD catheter

PD, Peritoneal dialysis.

Maintenance of Euvolemia

Achievement of euvolemia is an exceptionally important adequacy target because of the high prevalence of hypertension and cardiovascular disease in children receiving PD. Optimization of the fluid status requires knowledge of a patient's UF capacity and RKF. In patients who are hypertensive or in whom there is evidence of volume overload, UF should generally be positive for all daytime and nighttime exchanges. An effort should be made to determine the lowest possible dialysate dextrose concentration required to achieve the desired UF volume so as to help preserve peritoneal membrane function hopefully. This is best conducted with knowledge of the patient's peritoneal membrane transport capacity as derived from the PET. Patients who are characterized as high/rapid transporters and who are unable to achieve the UF necessary for blood pressure control with standard dialysis solutions should be considered candidates for the use of an icodextrin-based dialysis solution. Additional factors that may help maintain euvolemia include dietary sodium and fluid restriction and use of diuretics in patients with RKF, as was demonstrated by the International Pediatric Peritoneal Dialysis Network (IPPN). On the other hand, meticulous attention should also be paid to fluid and salt management in patients who are polyuric. These patients might need fluid and salt supplementation to minimize the risk for hypotension, which, during infancy, in particular, can be associated with severe ophthalmological and neurocognitive complications. It is thus reasonable to suggest that a targeted fluid status, rather than fluid removal, should be the primary goal for adequate dialysis therapy.

The impact of the APD prescription on daily UF volume was assessed in the IPPN cohort. From a total of over 7800 observations in nearly 2500 children, a mean daily UF volume of $600 \pm 680\ mL/m^2$ was achieved. After adjusting for age, time on PD, and RKF, UF volume was directly and significantly influenced by the average dextrose concentration (240 mL more UF per percentage increase in dextrose concentration), number of cycles, and both the daytime and nighttime fill volumes and was inversely associated with the dwell time (34 mL less UF per hour increase in dwell time; $p < 0.001$).

Timing and Frequency of Solute Clearance and Ultrafiltration Measurement

For patients initiating dialysis for the first time and/or patients with substantial RKF, the initial measurement of total (dialysis and RKF) clearance should be performed within 4 weeks of the initiation of PD. For patients transferring from another renal replacement therapy to PD and/or for patients who do not have substantial RKF, the initial measurement of the delivered dose of PD should ideally be made somewhat earlier, but only after the institution of target fill volumes, to help prevent a prolonged period of underdialysis. The measurement of total Kt/V_{urea} should be performed when the patient is clinically stable (e.g., stable weight, stable blood urea nitrogen [BUN], and creatinine concentrations) and should an early episode of peritonitis occur, at least 4 weeks after resolution of the infection.

The total solute clearance should be measured once during the first 6 months of therapy and at least every 6 months thereafter. As mentioned earlier, modification of the measurement schedule may be necessary if the dialysis prescription has been changed or there have been clinical events (e.g., protracted/repeated peritonitis) that may have altered the function of the peritoneal membrane. If achievement of the target Kt/V_{urea} for a patient is dependent, in part, on the contribution from RKF, KDOQI recommends that the measurement of RKF be performed a minimum of every 3 months until the residual Kt/V_{urea} is < 0.1, when its contribution to total clearance becomes negligible, and a change in the dialysis prescription to compensate for

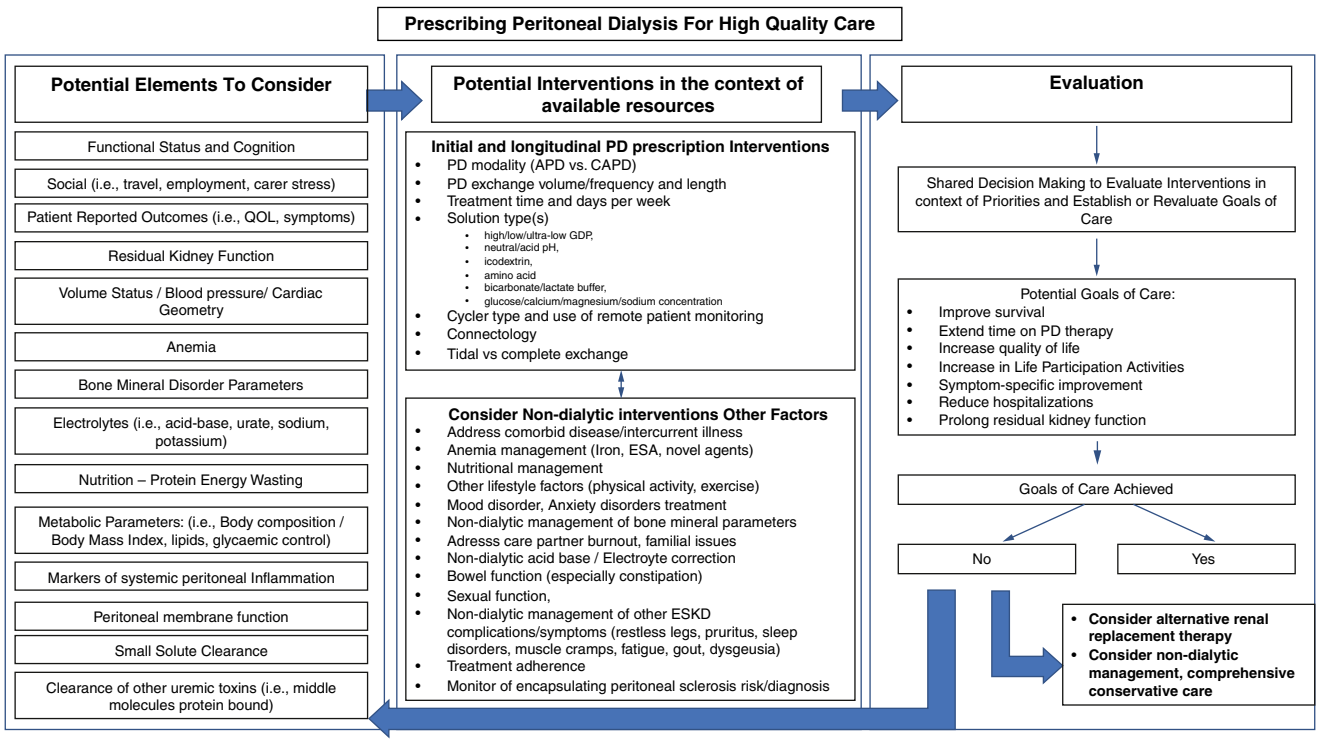
the loss of RKF should be instituted. Ideally, this should be followed by a repeat assessment of the solute clearance. Finally, the patients' record of PD effluent volume should be reviewed monthly with particular attention to the drain volume from the overnight dwell of CAPD and the daytime dwell of CCPD.

Adjusting the Dialysis Prescription by Computer Modeling

Computer-based dialysis modeling may help tailor the PD prescription to the desired solute removal, transport type, body size, lifestyle, etc. Kinetic modeling programs use peritoneal membrane transport capacity test data from the standard PET (PD Adequest, Baxter Healthcare) and the PDC test (PACK PD, Fresenius; CDC Gambro) to help in prescription management. These have been validated for clinical use in pediatrics. The major advantage of computer assistance is the flexibility and speed with which prescription options can be determined. Kinetic modeling may be especially important for APD therapies because of the variety of prescription modifications that are inherent to this modality. Whereas an increase in the fill volume is generally the most effective approach to increase the delivered dose of dialysis, computer-assisted kinetic modeling can also be used to determine the likely impact of changes in the exchange frequency or the addition of a daytime exchange, characteristics that influence dialysis adequacy and QOL. It needs to be emphasized that even with the use of computer assistance, actual solute clearance measurements are mandatory to confirm the delivered dialysis dose.

Summary

The adequacy of PD is only one aspect of the global management of the patient with ESKD. Clinicians formulating the PD prescription designed to achieve dialysis adequacy in children should be well versed in the properties of CAPD and APD, the value and limitations of Kt/V_{urea} as a measurement of adequacy, the assessment of peritoneal transport characteristics, and the use of computer technology to adjust the dialysis prescription. As in adults, it must be emphasized that the achievement of numeric targets should never be considered the sole determinant of adequate care. Kt/V_{urea} is only a measure of delivered dialysis dose, and achievement of a target value cannot and should not be equated with high-quality dialysis care. Instead, multiple measures and care goals, including clinical symptoms, RKF, volume status, biochemical measures, nutritional status, cardiovascular function, and sense of well-being in addition to solute clearance, all need to be considered when assessing the quality of dialysis care (Fig. 81.2).



• **Fig. 81.2** Algorithm for PD prescription management. *APD*, Automated peritoneal dialysis; *CAPD*, continuous ambulatory peritoneal dialysis; *ESKD*, end-stage kidney disease; *PD*, peritoneal dialysis; *QOL*, quality of life. (Reprinted with permission from Brown EA, Blake PG, Boudville N, et al. International Society for Peritoneal Dialysis practice recommendations: prescribing high-quality goal directed peritoneal dialysis. *Perit Dial Int*. 2020;40(3): 244-253.)

Recommended Reading

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Chadha V, Warady BA. What are the clinical correlates of adequate peritoneal dialysis? *Semin Nephrol.* 2001;21:480–489.

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Chadha V, Blowey DL, Warady BA. Is growth a valid outcome measure of dialysis in children on peritoneal dialysis? *Perit Dial Int.* 2001;21:S179–S184.

Single-center retrospective study of 24 patients demonstrating that RKF likely exerts significant influence on the linear growth in children.

Warady BA, Neu AM, Schaefer F. Optimal care of the infant, child, and adolescent on dialysis: 2014 update. *Am J Kidney Dis.* 2014;64(1):128–142.

Review of current clinical recommendations based on evidence and expert opinion pertaining to the care of the pediatric patient on dialysis.

Brown EA, Blake PG, Boudville N, et al. International Society for Peritoneal Dialysis practice recommendations: prescribing high-quality goal directed peritoneal dialysis. *Perit Dial Int.* 2020;40(3):244–253.

Latest ISPD guideline pertaining to care of the patient receiving PD. It emphasizes the importance of shared decision making between the patient and the care team, with an objective of goal-directed dialysis delivery.

Warady BA, Schaefer F, Bagga A, et al. Prescribing peritoneal dialysis for high-quality care in children. *Perit Dial Int.* 2020;40(3):333–340.

Latest ISPD guideline highlighting timing of dialysis initiation, modality selection, and PD prescription adjustment with the goal of achieving desired outcomes in children.

Paniagua R, Amato D, Vonesch E, et al. Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADMEX, a prospective, randomized, controlled trail. *J Am Soc Nephrol.* 2002;13:1307–1320.

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Lo WK, Ho YW, Li CS, et al. Effect of Kt/V on survival and clinical outcome in CAPD patients in a randomized prospective study. *Kidney Int.* 2003;64:649–656.

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Fischbach M, Warady BA. Peritoneal dialysis prescription in children: bedside principles for optimal practice. *Pediatr Nephrol.* 2009;24:1633–1642.

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Solute equilibration curves and mass MTAC values for children are reported and serve as reference data for performance of the PET in the pediatric PD population.

Haraldsson B. Assessing the individual peritoneal dialysis capacities of individual patients. A clinical tool based on the three pore model. *Kidney Int.* 1995;47:1187–1198.

Study describes the methodology and usefulness of measuring individual PD capacity based on the three-pore model.

Warady BA, Watkins SL, Fivush BA, et al. Validation of PD Adequest 2.0 for pediatric dialysis patients. *Pediatr Nephrol.* 2001;16:205–211.

Study evaluated the PD Adequest 2.0 for Windows program (Baxter Healthcare Co., Deerfield, IL) as a prescription aid for the management of pediatric PD patients.

Morgenstern BZ, Wuhl E, Nair KS, et al. Anthropometric prediction of total body water in children who are on pediatric peritoneal dialysis. *J Am Soc Nephrol.* 2006;17:285–293.

Study of total body water (TBW) measurement by heavy water ($H_2^{18}O$) dilution in pediatric patients (aged 1 month to 23 years) receiving chronic PD to establish and validate anthropometric TBW prediction equations.

Goldstein SL, Graham N, Burwinkle T, et al. Health related quality of life in pediatric patients with ESRD. *Pediatr Nephrol.* 2006;21:846–850.

Study presents the results of a pediatric ESRD-specific health-related quality of life (HRQOL) assessment instrument in pediatric patients with ESKD receiving hemodialysis, PD, or with a renal transplant.

Fischbach M, Zaloszyc A, Schaefer B, et al. Optimizing peritoneal dialysis prescription for volume control: the importance of varying dwell time and dwell volume. *Pediatr Nephrol.* 2014;29:1321–1327.

Review article explaining the impact of dwell time on UF and purification.

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Description of measurement of the hydrostatic intraperitoneal pressure as an objective approach to fill volume tolerance.

82

Continuous Renal Replacement Therapy in Pediatric Patients

IRFAN KHAN MD • PATRICK D. BROPHY MD, MHCDS

Introduction

Continuous renal replacement therapy (CRRT) is the preferred modality for the optimal management of fluid and electrolytes as well as nutritional support for children developing acute kidney injury (AKI) in the pediatric intensive care unit (PICU).[1]

Recent awareness about the association between fluid overload (FO) and adverse outcomes in patients with AKI has led to a practice change resulting in the earlier use of CRRT even with mild to moderate FO.[2] Despite the fundamentals of CRRT between adults and children being the same, there are some differences that exist in the utility of pediatric CRRT that relate to the size of the circuit, flow parameters, extracorporeal blood volume or blood priming, and vascular access.[3] Inborn errors of metabolism as an indication for CRRT are exclusive to the pediatric population.

CRRTs, either as continuous venovenous hemofiltration (CVVH) or hemodiafiltration (CVVHD), are used frequently in critically ill children. Improving recognition of AKI in younger patients and increasing comfort with providing CRRT for neonatal patients have led to a shift toward offering this therapy to this population.[4–7] Newly developed miniaturized machines like the Cardio-Renal Pediatric Dialysis Emergency Machine (Carpediem), the Newcastle Infant Dialysis and Ultrafiltration System (NIDUS), and Aquadex have shown success in the use of CRRT in critically ill neonates with extremely low birth weight (ELBW) as small as 800 g.

With the ever-increasing use of extracorporeal membrane oxygenation (ECMO) in children, the role of CRRT in combination and the potential complications that occur with its use need an understanding of the flow characteristics, the importance of circuit connections, and strategies to minimize complications.

Alternatives to CRRT like hemodialysis (HD) and peritoneal dialysis (PD) are not favorable for critically ill patients with hemodynamic instability. HD has the potential to also lead to disequilibrium, and PD can compromise the respiratory dynamics and is less effective in treating patients with exogenous intoxications and inborn errors of metabolism.

Indications and Options

The Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry is a multicenter collaborative registry that prospectively collected and analyzed data from children who received CRRT between 2001 and 2005 at 13 centers in the United States. They reported that 294/344 (86%) CRRTs were performed for FO, AKI, electrolyte abnormalities, or a combination of these.[8] The other 50 (15%) CRRT procedures were for nonrenal indications, of which 21 (42%) were for inborn errors of metabolism, 18 (36%) were for drug toxicity, and 11 (22%) were for tumor lysis syndrome.[9] Within these indications are use with patients on ECMO and liver failure molecular absorbent recirculating system (MARS).[10–12]

CRRT is composed of and refers to a variety of modalities, continuous arteriovenous hemofiltration (CAVH), continuous arteriovenous hemodialysis (CAVHD), continuous arteriovenous hemodiafiltration (CAVHDF), CVVH, continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF). Historically, continuous arteriovenous therapies were employed, but with the advent of newer machinery and techniques, their use has declined appropriately. We will, therefore, not address the continuous arteriovenous therapies further. Defining and understanding the terminology employed with these technologies require an appreciation for some of the basic concepts underlying their utility.

Diffusion and/or convection may accomplish transport of solutes across semipermeable membranes. Both methods of solute transfer occur in the normal mammalian kidneys, with diffusion occurring in the tubules and convection primarily occurring in the glomerulus.

Diffusion, which is the predominant method utilized in HD, CVVHD, and partly in CVVHDF, refers to solute movement across a membrane (down a concentration gradient), resulting in the same concentration on either side of the membrane.

Dialysis is, in fact, solute removal by diffusion of the solute across a membrane (however, in clinical settings, dialysis usually means a combination of diffusion and convection). During dialysis, the electrolyte solution (dialysate) runs in the opposite direction (countercurrent) to blood flow, separated by a semipermeable membrane.

The rate of mass transfer/diffusion is determined by the characteristics of the solute (size, charge, protein binding), the dialysis membrane (type, porosity, thickness, surface area), the rate of solute delivery (blood flow rate and dialysate rate, which in turn helps generate concentration gradient), and the gradient of substance in the dialysate to blood.

Diffusion removes substances < 20 kDa (urea, creatinine, uric acid, ions, interleukin-6 [IL-6], endotoxin, heparin, pesticides, ammonia, most protein-bound drugs) and causes less damage to platelets and leukocytes but poorly removes larger molecules.

Convection is the movement of molecules through a semipermeable membrane associated with the fluid being removed during ultrafiltration (UF). The solute molecule is swept through a membrane by a moving stream of ultrafiltrate. Convective transport is independent of solute concentration gradients across the membrane. The porosity of the membrane determines which solutes are removed. Positive pressure is generated in the blood compartment by increasing the hydrostatic pressure in the blood compartment and increasing the rate of blood flow to the membrane, or the negative pressure in the dialysate compartment facilitates UF, created by decreasing the oncotic pressure of plasma by predilution.

Convection is a more effective method for fluid removal for middle-sized molecules (< 60 kDa) removed (i.e., mediators in sepsis), for example, IL-8, tumor necrosis factor (TNF), IL-10, IL-6, complement, eicosanoids, platelet-activating factor, and myocardial depressants.

Convection, CVVH and partly by CVVHDF, refers to the movement of solute together with solvent by means of filtration across a semipermeable membrane. This occurs in response to a transmembrane (TMP) pressure gradient.[13,14]

1) Convection:
   Filtration is governed by Qf = Km TMP, where:
   Qf = filtration rate (mL/h), Km = membrane permeability coefficient, and TMP = transmembrane pressure (mm Hg) {TMP = Pb-Puf-p, where Pb = hydrostatic pressure of blood, Puf = hydraulic pressure of the dialysate/ultrafiltrate compartments and p = protein oncotic pressure}
   Solute transport is governed by Jc = $UF(x)_{uf}$, where:
   UF = ultrafiltrate volume and $(x)_{uf}$ = solute x concentration in the ultrafiltrate
   Convective treatment clearance is represented by Kc = $Qf(x)_{uf}/(x)_{Pw}$, where:
   Qf = UF rate and $(x)_{uf}/(x)_{Pw}$ = ratio of ultrafiltrate and plasma water solute concentrations (or the sieving coefficient [SC])
2) Diffusion:
   Solute transport is governed by Jd = DTA (dc/dx), where:
   Jd = solute flux, D = diffusion coefficient, T = solution temperature, A = membrane surface area, dc = concentration gradient between compartments and dx = membrane thickness

The generation of crystalloids and plasma water from whole blood across a semipermeable membrane in response to a TMP gradient is referred to as UF. During UF, passage of solutes across the membrane is based on their membrane SC.

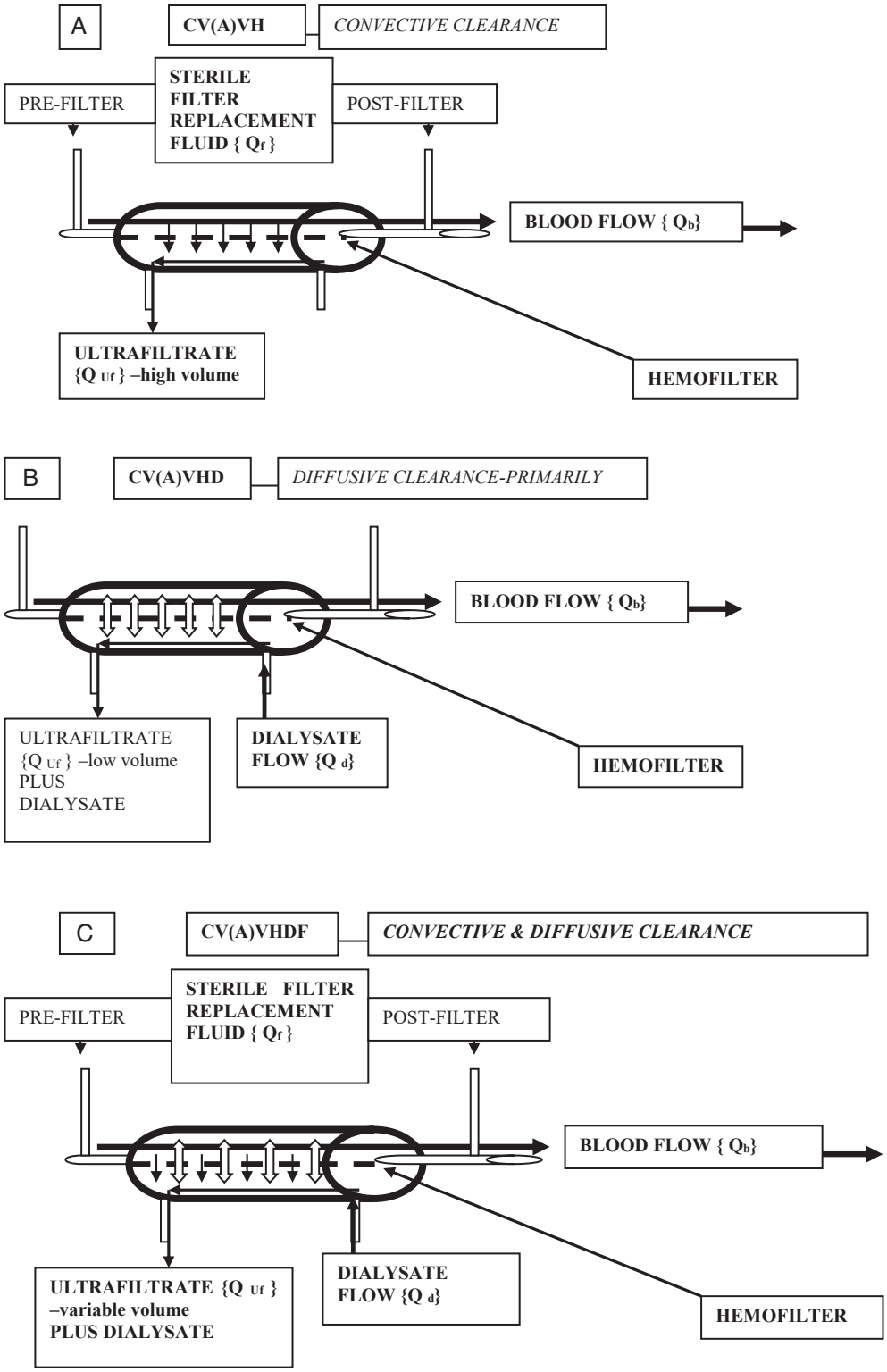
SC is the ratio of the concentration of solutes in the ultrafiltrate to that of plasma. A high SC is desirable for middle molecules but undesirable for albumin sized molecules.

SC = 1—describes complete permeability (for urea and creatinine)
SC = 0—reflects complete impermeability
SC > 1—requires an external energy source

During UF, the driving pressure forces solutes (such as urea and creatinine) against the membrane, and the solutes penetrate the pores of the membrane to an extent determined by the membrane SC for that molecule. Major factors determining SC include solute molecular size, protein binding, and filter porosity.

CVVH utilizes convection almost exclusively along with high UF rates. The ultrafiltrate produced is replaced completely or in part by sterile filter replacement fluid (Qf), also referred to as FRF. Patient weight loss results from the difference between UF and reinfusion rates. Replacement fluid can be administered either pre-membrane filter (predilutional) or post-membrane filter (postdilutional) (Fig. 82.1A). Predilutional replacement is preferred for venous-venous circuits as it decreases the blood viscosity and may improve filter longevity as well as decrease anticoagulant requirements. Postdilution replacement is preferred for arteriovenous circuits and may result in improved solute clearance. Solute clearance is dependent on membrane surface area and blood flow rate. Accordingly, any factors that influence these parameters ultimately affect the efficiency of the prescription.[15,16]

CVVHD offers primarily diffusive solute clearance through the use of dialysis fluid (Qd). The variables in solute clearance are blood flow, membrane surface area, and dialysate rate, but some convective clearance occurs with low-volume UF. The low-volume UF is directly related to fluid removal titrated to the desired patient weight loss plus removal of obligate fluids (medication drips, total parenteral nutrition [TPN], etc.) being provided to the patient. The general principles governing CRRT clearance are based on the same properties as intermittent HD (IHD). The dialysis fluid may be commercially made or custom made. In many cases, the components of the dialysate are identical to the filter replacement fluid utilized in CVVH (Fig. 82.1B).



• **Fig. 82.1** (A) Continuous Venovenous hemofiltration. (B) Continuous venovenous hemodialysis. (C) Continuous venovenous hemodiafiltration.

CVVHDF offers both convective and diffusive solute clearance through the combination of dialysis fluid (Qd) and filter replacement fluid (Qf). This combination technique may offer an improved clearance rate of some intoxicants and middle molecules. Once again, fluid balance can be maintained or titrated to the desired rate by the administration of a sterile solution. Replacement fluid can be administered either pre-or postfilter. In this case, the UF rate would tend to be intermediate between the high volume seen in CVVH and the low (minimal) UF rate seen in CVVHD (Fig. 82.1C).

Continuous Venovenous Therapies

With the development of new CRRT machines,[17] the problems of infusion pump errors as well as manual effluent bag measurements seem a thing of the past. With the safer and more accurate UF control than past adapted machines, CVVH(DF), rather than CAVH(DF), has become the preferred method of CRRT for pediatric patients at most centers. These therapies are effective when the patient is unable to generate a significant arteriovenous pressure difference (i.e., cardiac failure), and they also offer the advantage of requiring one single dual-lumen access. The larger circuit volumes associated with CVVH(DF) may be problematic when initiating therapy in smaller infants or neonates. Generally, an attempt is made to keep the extracorporeal circulating blood volume <10% of the infants' total blood volume. In cases where greater than 10% of the patient's blood volume is extracorporeal, whole-blood priming is utilized at the initiation of treatment, thereby decreasing potential hemodynamic compromise. Currently, technology in the pump-assisted system offers multimodality use (i.e., CVVHDF), blood pumps and air leak detectors, venous pressure monitors, and relatively straightforward computerized menus for easy troubleshooting.[15] The initial offering for integrated machinery was put forth by Gambro (now Baxter International, Deerfield, IL, USA). This spurred the development and distribution of a variety of machine offerings from other critical-care-focused companies. Other significant considerations besides CRRT machine choice include membrane choice, tubing, and vascular access. Many of the available machines now have pediatric lines and filter sets. The newer systems also offer increased mobility and, therefore, improve potential application of these modalities in settings other than the intensive care unit (ICU) (Brophy, McBryde, Mottes, Dorsey, Adams and Bunchman 2000). As with all things in health care, these machines are expensive,[18] which may make their use in smaller centers or less industrialized nations difficult.

Prescription

Unlike chronic dialysis, there are no standard recommendations for targeted clearance (i.e., Kt/V). Intuitively, improved dialysis clearance would be associated with improved patient outcomes, although the data supporting this belief is limited. CVVH or CVVHD(F) offers excellent modes of continuous dialysis and are generally equally effective, with CVVH having some potential advantages for middle molecule clearance. The choice of modality is dependent, in part, on the method of anticoagulation and solutions used[19] (Laliberte-Murphy, Palsson, and Niles 2001), as well as institutional pharmacy policies.

The rate of dialysis (Qd) with or without filter replacement fluid (Qf) can be referred to as the dialysis dose. The optimal dialysis dose is not known and likely varies depending on the clinical situation. There has been a trend toward increased dialysis dose rates in adult patients at the initiation of CRRT. Historically dialysis dose rates in adult centers were 1 L/h, but now typical prescriptions have flow rates between 1.5–2.0 l/h[20] (Clark and Ronco 2000). Ronco et al.[20a] demonstrated that in adult patients with AKI, a Qf of at least 35 mL/h/kg was associated with improved patient survival. A subset of these patients was reevaluated, and in the setting of sepsis, a Qf of 45 mL/kg/h was associated with improved patient survival. Subsequently, two larger randomized trails, the RENAL and the ATN studies did not support an improved outcome with higher Qf rates. The inflammatory cascade in sepsis has become the target of recent treatment goals. Human studies have demonstrated that using high-volume hemofiltration (HVHF), targeting removal of either inflammatory or inciting molecules, decreased vasopressor requirements with trends toward improved survival in adult septic patients.[21–24] Ratanarat et al.[25] provided more support that pulse HVHF is effective in improving hemodynamic stability and improved survival in the septic patient. The Qf was 85 mL/kg/h for 6–8 hours daily until clinically stable. Pulse therapy appears to provide a similar outcome to 24-hour continued HVHF, with much less financial burden and workload on the support staff. The maximum Qf may be limited by the total UF rate allowed by the dialysis filter. In most children, achieving dialysis dose rates comparable to 35–45 mL/kg/h is readily obtainable. The author's prescription in the setting of sepsis often consists of CVVHDF for the first 48–72 hours, with Qf 75% and Qd 25% of the total dialysis dose of 4 L/h/1.73 m^2. After this time period, therapy is transitioned to either CVVHD or CVVH, with a dialysis dose of 2 L/h/1.73 m^2.

While published guidelines for the implementation of pediatric CRRT do exist,[16] most centers providing CRRT to children base it on their own experience and needs. The authors' standard prescription for CVVHD has a blood flow rate of 3–5 mL/kg/min,[26] with higher blood flow rates (6–10 mL/kg/min) being used in patients for whom anticoagulation is contraindicated or for whom high clearance rates are desirable. Filter replacement fluid (Qf), either pre- or postfilter or countercurrent dialysate (Qd), is delivered at 2 L/h/1.73 m^2. Indications for adjustments in dosing are addressed in the prior paragraph. Even though CVVHD is primarily a diffusion-based therapy, the prescriber must remember that some degree of convection therapy is present because of prescribed net fluid removal and removal of ongoing intravenous fluids being provided to the patient. Goldstein et al.[27] described a mean contribution of 17% convection clearance to the total dose of dialysis in patients on CVVHD. Fluid removal is usually between 0.5 and 2.0 mL/kg/h, depending on patient volume status and hemodynamics. This rate is a direct extrapolation of work on HD by Donckerwolcke and Bunchman,[28] who demonstrated this to be a safe and effective UF rate in pediatric HD. We have found that in some severely edematous patients, increasing pressor support to permit safe UF can be helpful in the initial 24–48 hours of CRRT, resulting in improved cardiac and pulmonary function as the patient's degree of volume overload is reduced.

As in HD, the extracorporeal volume of the CRRT circuit should be <10% of the patient's blood volume. Patients less than 10 kg have blood volumes of about 80 mL/kg, while larger children have blood volumes closer to 70 mL/kg. Under circumstances where the patient's circuit volume is in excess of 10% of the patient's total blood volume, blood priming often becomes necessary. The packed red cells obtained from most blood banks possess a high hematocrit (HCT) level (around 50%–60%) and need to be reconstituted to around 30% with 0.9% saline in order to avoid clotting the circuit. Anticipation of the potential for the development of hypothermia in youngsters with a significant portion of their blood volume in the extracorporeal space is imperative. Under these circumstances, the use of patient warmers, heating pads applied to the circuit tubing, or manufactured blood warmers should be utilized.

Access

A working vascular access is essential for performing CRRT efficiently and without interruption. Dual-lumen temporary HD catheters are the catheters of choice, although tunneled catheters can also be utilized if therapy is expected to be prolonged. HD catheters must be inserted under ultrasound guidance by trained personnel, using aseptic conditions. The right internal jugular (IJ) vein is the preferred site. The primary goal of vascular access for CRRT is to have adequate flow to provide optimal therapy. In general, one wants to maintain a venous pressure of no more than 200 mm Hg. While recirculation is commonly discussed with HD, this is less of an issue due to the continuous nature of CRRT. Classically, dual-lumen catheters (venous therapies) were enough for CRRT, but with the trend toward citrate anticoagulation, double-lumen access with an additional separate central line has become necessary. The desirability for the additional central line has arisen due to the need for an independent line for calcium infusion back to the child when citrate anticoagulation is used in CVVHD (see section on anticoagulation). The calcium can be Y-into the venous/return line of a double lumen dialysis catheter if the catheter is 14 Fr (French) or larger; otherwise, our experience has demonstrated an increased risk of clotting in the venous/return port.

Many nephrologists prefer to avoid using subclavian catheters because of the risk of subclavian stenosis, as some patients may develop end-stage renal disease requiring a fistula in the future. The advantage of the IJ catheter is that it is independent of the patient's motion and appears to give adequate blood flow with insignificant resistance. The historical disadvantages of the IJ catheter leading to a pneumo or hemothorax at the time of placement are less with the advent of vascular ultrasound-guided placement. The femoral line may have less complication risks at the time of placement compared to a "high line"; however, the disadvantages are risk of thrombosis of the vein, complicating future renal transplant options, and coming to light in the face of an awake and moving patient. When the access becomes kinked or moved, blood flow to the CRRT circuit is inhibited, with a subsequent increased risk of circuit clotting and decreased delivery of dialysis dose. For an excellent review of pediatric access and complications, see Hackbarth et al.[3]

Blood flow rates for CRRT are determined by the size of the child, the machine utilized, and the vascular access pressures. Flow characteristics of vascular access demonstrate that a short, large-bore access has less flow resistance (and potentially improved performance) compared to a longer, smaller internal-lumen access.[29] Blood flow rates range from 10 to 50 mL/min in the infant <5 kg, 30 to 85 mL/min in the child 5–15 kg, 50 to 125 mL/min in the child 15–25 kg, and often 100 to 250 mL/min in the larger child. Historically, umbilical vein (UVC) and artery (UAC) catheters in the newborn were utilized. However, with the newer generation of CRRT machines, which have less forgiving venous and arterial pressure alarms, the use of a UVC or UAC is less effective due to their high resistance.[30] Many accesses are available for larger (i.e., >40 kg) children, but in the smaller sized individual, single-lumen 5 Fr is the smallest line that will allow for continuous therapies (Table 82.1).

A very common occurrence is the development of high (negative) arterial and/or venous pressures when the blood

TABLE 82.1 Suggested Size and Selection of CRRT Vascular Access for Pediatric Patients

Patient Size	Catheter Size and Source	Site of Insertion
Neonate	Single-lumen 5 Fr (COOK)	Femoral artery or vein
	Dual-Lumen 7.0 Fr (COOK/MEDCOMP)	Internal/external-jugular, subclavian, or femoral vein
3–6 kg	Dual-Lumen 7.0 Fr (COOK/MEDCOMP)	Internal/external-jugular, subclavian, or femoral vein
	Triple-Lumen 7.0 Fr (MEDCOMP, ARROW)	Internal/external-jugular, subclavian, or femoral vein
6–30 kg	Dual-Lumen 8.0 Fr (KENDALL, ARROW)	Internal/external-jugular, subclavian, or femoral vein
>15-kg	Dual-Lumen 9.0 Fr (MEDCOMP)	Internal/external-jugular, subclavian, or femoral vein
>30 kg	Dual-Lumen 10.0 Fr (ARROW, KENDALL)	Internal/external-jugular, subclavian, or femoral vein
>30 kg	Triple-Lumen 12 Fr (ARROW, KENDALL)	Internal/external-jugular, subclavian, or femoral vein

CRRT, Continuous renal replacement therapy.

pump attempts to deliver the prescribed blood flow rate to the circuit. If relatively simple interventions (i.e., repositioning the catheter or the patient) do not correct this problem promptly, a prolonged period of blood stagnation in the circuit occurs, potentially leading to clotting, treatment interruption, and circuit loss. Proper nursing management of catheters is crucial, not only in avoiding these complications but also in ensuring that appropriate hygienic measures are taken to minimize infection risk. The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) AKI guidelines recommended the sites of catheter placement by order of preference: right IJ vein > > femoral vein > left IJ vein > subclavian vein (dominant side) > subclavian vein (nondominant side).

Solutions

Consideration of both convective (CVVH) as well as diffusive (CVVHD) therapies (see sections on prescriptions and anticoagulation) needs to be made when determining what type of solution to employ. Presently, the utilization of countercurrent dialysis solution vs. filter replacement fluid or both is based on the local standard of care.

The Food and Drug Administration (FDA) considers anything that is placed into the vascular space a drug. Due to complications associated with lactate-based solutions (i.e., a lactate load to the patient can result in rising plasma lactate levels, which may erroneously indicate a poor perfusion state), the initial FDA-approved solution for sterile bicarbonate–based replacement fluid was Normocarb (Dialysis Solution Inc., Richmond Hills, Ontario, Canada). This prototypical solution provided the impetus for other companies to develop a variety of replacement fluid offerings that are now also FDA approved. Modern physiologic solutions include varying bicarbonate levels. These may be calcium or phosphate based, and their use is guided by the patient's particular circumstance and choice of anticoagulant strategy used.

Local pharmacy-made solutions do not have industry standards of quality assurance, and programs have reported fatal or near-fatal complications due to errors in the components of the pharmacy-made solutions[31] (Table 82.2).

Dialysis solutions are not considered drugs but rather devices (Table 82.3). This is because these are not infused intravascularly. The FDA has therefore approved them for use in CVVHD. Presently, within the United States, there are multiple solutions that are FDA approved for dialysis, and the same applies to other areas worldwide. Alternatively, pharmacy-prepared bicarbonate-based customized solutions may be employed. The authors would recommend bicarbonate concentrations of 25 mEq/L in custom solutions. If acidosis needs to be aggressively treated, then we would recommend a separate sodium bicarbonate drip (150 mEq/L $NaHCO_3$) infusing the patient at 40–80 mL/m^2/h. These custom solutions may be phosphorus based or calcium based. If phosphorus-based solutions are employed, calcium must be infused directly into the patient. With calcium-based solutions, phosphorus must be infused into the patient as part of the TPN or separate continuous infusions.

In general, commercially based bicarbonate-based solutions are regularly employed. The rationale behind lactate-based solutions is not physiologic but has to do with the permeability of the plastic bags and solution stability. Plastic bags that contain the solutions for either PD or CRRT solutions are permeable to CO_2, and over time bicarbonate will break down to H_2O and CO_2, with a subsequent loss in buffering capability. Lactate does not decompose, and, therefore, these solutions remain stable. In current technology, with a

TABLE 82.2 General Comparison of Custom-Made vs Standard Commercially Available Solutions

Premade Solutions Additives	Ringer Lactate	1.5% PD Fluid	Custom-Made Solution Additives	Calcium-Based FRF/Dialysate	Phosphate-Based FRF/Dialysate
Na (mEq/L)	130	132	NaCl (mEq/L)	110	110
K (mEq/L)	4	0	$NaHCO_3$ (mEq/L)	25	25
Cl (mEq/L)	109	96–102	KCl (mEq/L)	0–4	0–4
HCO_3 (mEq/L)	0	0	Na_3PO_4 (mmol/L)	0	0–2
Lactate (mEq/L)	28	40	Lactate (mEq/L)	0	0
Ca (mEq/L)	3	3.5	$CaCl_2$ (mEq/L)	3.5	0
PO_4 (mEq/L)	0	0	$MgSO_4$ (mEq/L)	1.5	1.5
Mg (mEq/L)	0	0.5–1.5	Dextrose (g/L)	1.5 (0.15%)	1.5 (0.15%)
Dextrose (g/L)	0	15			
			Solutions are mixed with sterile technique in the pharmacy (Sterile water used as a base)		

FRF, Filter replacement fluid.

TABLE 82.3 Comparison of Common Dialysis Solutions

Electrolyte (mmol/L)	Normocarb (DSI)	PrismaSate(Gambro)			ACCUSOL (Baxter)	Duosol (Braun)	Custom (Pharmacy)
		BK0/3.5	BKK2/0	B25GK4/0			
Na (mEq/L)	140	140	140	140	140	140	135
Ca (mEq/L)	0	3.5	0	0	3.5	3	0
K (mEq/L)	0	0	2	4	0–4	0–4	0–4
Mg (mEq/L)	1.5	1	1	120.5	1.0–1.5		1.5
Cl (mEq/L)	107	109.5	108	120.53	109.5–116.3	109–113	110
Phos (mmol/L)	0	0	0	0	0	0	0.75–1.50
L-lactate (mEq/L)	0	3	3	3	0	0	0
Bicarb (mEq/L)	25/35	23/32	23/32	22	30–35	35	25
Glu (mg/dL)	0	0	110	110	0-100		0
FDA OK	Y (D&FRF)	Y (D)			Y(D)	Y (D)	N (D&FRF)

Not all are inclusive of the various formulas available and recommend visiting each individual company's website or directly contacting the company for complete information.
D, dialysate (Qd); *FRF*, filter replacement fluid (Qf).

two-compartment bag, the bicarbonate solution is located in a separate compartment and directly attached via a breakable connector to the larger solution bag, which contains the remaining elements. When the time comes to use the solution bag, the seal is broken and allows for the mixing of the bicarbonate with the rest of the solution. The breaking of this seal and complete mixing of the solution are imperative as reports of severe metabolic acidosis have been documented. Most commercial solutions now use this approach.

With the use of a lactate-based solution, lactate is delivered to the patient.[32] These solutions can be associated with rising lactate levels in patients, making it difficult to discriminate whether this lactate level is related to lactate from the patient or lactate from the solution. Recently, some solutions are comprised of L-lactate, making it impossible to discriminate based on testing for the various isoforms. Since both "levo" and "dextro" lactate isoforms exist, in some situations, one could discriminate between the endogenous and the solution-derived lactate; however, most institutions do not have the reference lab capability to turn these results around in a timely and, therefore, clinically relevant fashion. Comparison data to date demonstrate that bicarbonate solution for CRRT not only is more physiologic but also is associated with improved outcomes, has less associated patient hemodynamic instability, decreases vasopressor requirements, and lessens the need for bicarbonate replacement when compared to lactate-based buffer solutions.[32,33] A Cochrane database of systematic intervention-based reviews in 2015 demonstrated that there was no significant difference between bicarbonate- and lactate-buffered solutions for mortality, serum bicarbonate levels, SCr, serum base excess, serum pH, carbon dioxide partial pressure, central venous pressure, and serum electrolytes. Patients treated with bicarbonate-buffered solutions, however, may experience fewer cardiovascular events, lower serum lactate levels, higher mean arterial pressure, and less hypotensive events. Overall, there was insufficient evidence to support a clinical advantage for either bicarbonate- or lactate-buffered solutions for acute continuous hemodiafiltration (HDF) or hemofiltration (HF).[33]

Anticoagulation

Activation of the clotting cascade occurs in CRRT circuits due to the contact of the circulating blood with artificial surfaces. Low blood flow rates, turbulent blood flow, and high HCTs hasten this effect. The delivery of an effective dialysis dose in CRRT depends on adequate anticoagulation of the extracorporeal circuit. In most patients, either systemic heparin anticoagulation (SHA) or regional citrate anticoagulation (RCA) is used.

The basic principle of RCA is to reduce the level of ionized calcium in the extracorporeal circuit via infusion of citrate. This way, effective anticoagulation restricted to the extracorporeal circuit is achieved. Citrate anticoagulation has gained acceptance due to its ease of administration and low patient side effect profile compared to heparin.[19,34–43]

Infusing citrate postpatient and prefilter allow regional anticoagulation of the CRRT system. Citrate binds with the serum calcium, making the CRRT system hypocalcemic, minimizing calcium-dependent clotting. Patient hypocalcemia is avoided by infusing calcium back into the patient independent of the CRRT system.

Citrate is cleared by the tricarboxylic acid pathway in the liver, skeletal muscles, and renal cortex, producing bicarbonate. Citrate carries the risk of hypocalcemia when it

is insufficiently metabolized and thus accumulates. Also, metabolic acidosis may develop when citrate is insufficiently metabolized, while metabolic alkalosis develops when too much citrate enters the circulation and is subsequently metabolized. Moreover, when calcium-free replacement fluids are used, calcium supplementation is required.

Citrate anticoagulation can be rationalized into two processes. The first process is to titrate the citrate anticoagulation going into the system to target the CRRT system ionized calcium between 0.25 and 0.40 mmol/L immediately postfilter. The second process is to deliver calcium back to the patient to target the patient's calcium to a physiologic level between 1.10 and 1.30 mmol/L. While many protocols exist, either a 4% trisodium citrate (TSC) solution or an ACD-A (Baxter Healthcare, Deerfield, IL) solution is available. An equimolar amount of ACD-A has a lower amount of citrate (67% TSC and 33% citric acid) compared to TSC, resulting in a lower risk of metabolic acidosis. Hypernatremia is less common with the use of ACD-A (220 mEq/L) solution compared to the 4% TSC solution (440 mEq/L), which requires a custom-made calcium-free hyponatremic (117 mEq/L) dialysis solution.[35]

Citrate toxicity occurs when the delivery rate of citrate exceeds the clearance rate. The clearance rate of citrate, SC is like urea (0.88–1.00),[44] and is related to both the clearance properties of the hemofilter (either convective or diffusive) as well as hepatic metabolism. This phenomenon, termed "citrate lock," becomes apparent when the patient's total calcium (albumin-calcium complex + citrate-calcium complex + ionized calcium = total calcium) rises while the patient's ionized calcium is stable or dropping. Citrate levels can be measured, but these tests are not easily obtainable. A ratio of total calcium to ionized calcium (both in units of mg/dL) >2.5 supports the diagnosis of "citrate lock." If this phenomenon occurs, then the citrate infusion is discontinued for 15–30 minutes and reinitiated at 70% of the previous rate. Citrate can be used in hepatic insufficiency, but then the normal rate of the initial citrate infusion should be 50%–70% of a "routine" rate with the same monitoring as in patients with normal hepatic function. Hyperglycemia is more frequent in smaller infants because of the glucose in the ACD-A solution (2.45 gm/dL), and these patients require adjustment in the dextrose of the TPN and possibly concomitant insulin infusion. Metabolic alkalosis can easily be corrected by decreasing the citrate infusion rate, increasing the dialysate rate to increase the clearance of citrate, or infusing back an acidotic solution (i.e., 0.9% normal saline (NS), pH 5.4–5.8, starting at 25% citrate rate) back to the patient. For example, many programs use citrate anticoagulation with a bicarbonate-based solution such as Normocarb, which can also add to the development of metabolic alkalosis. By adding in a replacement fluid (i.e., change to CVVHDF mode) of normal saline (pH of 5.4), one can easily correct this metabolic alkalosis due to the low-grade acid (NS) exposure provided to the patient. This assumes the ability to increase removal of pCO_2 by the pulmonary system. If the patient is on TPN, then consider adjusting the chloride-to-acetate ratio.

Unfractionated systemic heparin remains a commonly used anticoagulant for CRRT. It is relatively easy to use and monitor and provides adequate extracorporeal anticoagulation. However, the risk of bleeding and development of heparin-induced thrombocytopenia (HIT) are important drawbacks.

Heparin is infused in the CRRT system prefilter and is used to anticoagulate the system. Heparin's anticlotting potential is then measured by measuring a postfilter partial thromboplastin time (PTT), anti-Xa level, or an activated clotting time (ACT). The advantage of measuring ACT is that it can be monitored at the bedside with a rapid turnaround time. Heparin monitoring targets an ACT between 180 and 220 seconds or the PTT between one and a half to two times normal. This is usually accomplished by initially giving 20–30 units/kg bolus followed by a continuous drip of 10–20 units/kg/h of heparin.[30,45] The advantage of heparin is the historical use and familiarity by many nephrologists. The disadvantage of heparin is that it is infused into the patient and can be associated with anticoagulation of the patient. Further, heparin can be associated with HIT, which can facilitate an increased risk of bleeding. In many patients with multi organ system failure (MOSF) requiring renal replacement therapy (RRT), systemic heparinization may be a detriment and should be avoided.

In one study,[46] low-molecular-weight heparin was compared to regionally administered citrate in postdilutional CVVH. Interestingly, citrate treatment reduced mortality, which could be partly explained by less bleeding, suggesting improved biocompatibility for citrate as compared to heparin-based CVVH. On the contrary, another trial comparing unfractionated heparin to citrate in predilutional CVVH did not show a survival benefit for citrate.[47] Two meta-analyses on this topic showed no difference in mortality; however, citrate reduced the risk of bleeding and was more efficacious in one of them.[43,48]

Regional heparin anticoagulation is also an option. However, a randomized controlled trial of Regional Citrate Versus Regional Heparin Anticoagulation for Continuous Renal Replacement Therapy in Critically Ill Adults demonstrated that RCA prolongs CRRT circuit life compared with regional heparin anticoagulation, does not affect cytokine levels, and is associated with fewer adverse events.[49]

Deep et al.[49a] have employed a very successful prostacyclin-based anticoagulation in children with fulminant hepatic failure. In their hands, it appears that prostacyclin is superior to other forms of anticoagulation, particularly in the setting of fulminant hepatic failure with improved circuit life and less systemic anticoagulation risk to the patient. This protocol offers another option for those interested in exploring an alternative anticoagulation strategy.

The use of no anticoagulation has been shown time and time again to be fraught with a shorter circuit lifetime as well as a high risk of clotting in general.[34] The approach of no anticoagulation is typically used in a patient with disseminated intravascular coagulopathy (DIC) who has a low platelet count with evidence of a sustained coagulopathy.

Many of these patients have a paradoxical coagulopathy, which would benefit from regional anticoagulation to prevent the CRRT system from clotting. Further, many of these patients are on continuous fresh frozen plasma replacement as well as platelet infusions to correct the underlying anticoagulation problem, which will, in turn, promote clotting of the CRRT system.

Hemofilter Membranes

An RRT membrane is a semipermeable filter with pores of approximately 35,000 Da. A logarithmic, linear relationship exists between molecular weight (MW) cut-off and membrane pore size. Along this membrane, the diffusion and convection processes can take place. Diffusion follows a concentration gradient (as in IHD) and is the ideal method to remove small (< 500 Da) molecules such as creatinine. Convection follows a hydrostatic pressure gradient (as in CVVH) and is the best method to remove middle-large (between 500 Da and 60 kDa, such as the 13,750-Da beta-2 microglobulin) and large (between 60 and 100 kDa, such as the 70-kDa albumin) molecules. When diffusion and convection are used simultaneously in continuous mode, this is called CVVHDF.[50]

A simple polysulphone hemofilter is suitable for a vast majority of patients. This membrane is robust, cheap, and resistant to contamination (less hydraulic membrane permeability loss). In contrast with the high-adsorbent polyacrylylnitrile (PAN) membranes, polysulphone membranes also do not adsorb antibiotics, which facilitates antibiotic adaptation during CRRT.[51] Commercially available hemofilters are chosen based on the equivalent surface area related to the patient's weight (see Tables 82.4 and 82.5).

Filter life of most membranes (even under RCA) is improved after soaking them with 5,000 IU/L unfractionated heparinn (UFH). In the UFH era, it was recommended to change the membrane every 24 to 48 hours, guided by filter pressure drop and TMP increase. RCA, however, enables maintaining filter porosity for up to 72 or 96 hours.

TABLE 82.4 Filters Only (Not Connected to Tubing)*

Patient Size (kg)	Hemofilter	Membrane Material	Surface Area (m^2)	Filter Priming Volume (mL)†
< 10	Minifilter Plus	Polysulfone	0.07	15
> 10	HF 400		0.30	28
> 20	HF 700		0.71	53
> 30	HF 1200		1.25	83
> 35	HF 2000		1.98	132
> 10	PAN 0.3	Poly-acrylonitrile	0.3	33
> 20	PAN 0.6		0.6	63
> 30	PAN 1.0		1.0	87

* This is a sample of various filters available in the United States. Please see a manufacturer's filter specification sheet for complete details.
† The arterial and venous line volumes vary depending on manufacturer. For example, adult lines (110 mL) and pediatric lines (64 mL) are available to use with the HF series.

TABLE 82.5 Filter Systems (Filter Attached to Venous and Arterial Tubing)*

Patient Size (kg)	Hemofilter	Membrane Material	Surface Area (m^2)	Filter Priming Volume (mL)	Set Volume (mL)
< 5	M 10	Acrylonitrile and sodium metthallyl sulfonate copolymer†	0.042	3.5	50
> 5	M 60		0.6	42	84
> 15	M 100		0.9	65	107
> 8	HF 20		0.2		60
> 20	HF 1000	Poly-arylethersulfone	1.15		165
> 30	HF 1400		1.40		186

* This is a sample of various filters available in the United States. Please see a manufacturer's filter specification sheet for complete details.
† AN-69 membranes.

The filtration fraction (FF) represents the percentage of plasma that is removed as UF and then replaced by substitution fluid. Under UFH anticoagulation, FF should remain between 16% and 20% to avoid filter clotting. RCA allows FF levels up to 30%–33%.

The SC is the ratio of UF to plasma solute concentration. Major factors determining the SC are solute molecular size, protein binding, volume of distribution, and filter porosity (Matson et al. 2004).

In the pediatric and neonatal setting, a membrane change must be performed when TMP exceeds 450 mm Hg. This is because the membrane has a much smaller surface and thus needs and tolerates a higher TMP.[52]

Un(protein)bound and low-MW (<500 Da) drugs are removed (e.g., salicylates, methanol, ethylene glycol, barbiturates, lithium, penicillin, carbapenems, aminoglycosides, cephalosporins, vancomycin, metformin, etc.).[53]

Protein-bound agents, high-MW drugs, and drugs with a high volume of distribution are not removed (e.g., digoxin, tricyclic antidepressants, phenytoin, benzodiazepines, beta-blockers [except atenolol], etc.).[53]

High-flux membranes have a larger pore size and thus increase the clearance by allowing larger molecules to pass through the membrane (at least in theory) as well as more UF flow for the same TMP. Almost all novel biocompatible CRRT membranes are of high-flux type.

Endotoxin induces an inflammatory response, with the secondary release of cytokines, which can progress to shock and multiple organ failure. In a randomized crossover double-blind study, CRRT with the oXiris filter seemed to allow effective removal of endotoxin and TNF-α, IL-6, IL-8, and interferon-γ (IFN-γ) in patients with septic shock–associated AKI. This may be associated with beneficial hemodynamic effects.[54]

Both hemofilters and HD membranes have improved in terms of biocompatibility over the past decades. Himmelfarb et al.[55] compared the use of biocompatible membranes (BCMs) and bioincompatible membranes (BICMs) in randomized acute physiology and chronic health evaluation (APACHE) scored patients with AKI. Significantly, 57% of patients treated with the BCM survived vs. 46% of patients treated with the BICM.[55] Also, 64% of patients in the BCM group recovered renal function, whereas only 43% of patients in the BICM group did. Individuals who were nonoliguric at the onset of dialysis did markedly better than those with oliguria. The increased use of BCMs, such as the AN-69[56] (polyacrylylnitrile membrane), in CRRT, while improving complementation activation and overall patient outcome, has led to the recognition of an entity termed "bradykinin release phenomena." This occurs due to membrane coactivation of Pre-kallikrein and Hageman factor(s), with the resultant production of bradykinin (a potent vasodilator) (Renaux and Thomas 1996). This "membrane reaction" is potentiated by the presence of angiotensin-converting enzyme inhibitors[57] and is exquisitely pH dependent. In pediatric patients requiring blood priming, this represents a potential cause of hypotension, as most blood bank blood has a low pH (~6.3) and contains bioactive components required to trigger the bradykinin release phenomena. Our approach to this reaction has been to buffer the blood prime, thereby increasing the pH to around 7.4, or by bypassing the hemofilter by giving the blood postfilter and synchronizing a saline prime of the filter at the same time. Along with the judicious use of bicarbonate boluses, these techniques have essentially eradicated this phenomenon in our institutions.[58] Interestingly, ionized calcium measurements have been normal in these patients, suggesting that the low pH rather than electrolyte abnormalities were responsible for this phenomenon.

Nutrition

Children with AKI often have a component of inadequate nutrition. Clinical guidelines for nutrition adaptations during CRRT are lacking. Current recommendations regarding nutrition support in pediatric CRRT must be extrapolated from adult studies.

CRRT has a direct and substantial impact on metabolism. In critically ill patients undergoing CRRT, energy requirements are estimated according to generally accepted rules, which have been elaborated for a broad population of patients. Most guidelines recommend indirect calorimetry, considered to be the gold standard.[59] The TICACOS study has confirmed that indirect calorimetry is superior to formula-based calculations.[60] Indirect calorimetry is the preferred method to assess resting energy expenditure (REE). Moderate underestimation of REE is common but not clinically relevant. Formula-based calculation of REE is inaccurate and not validated in critically ill children on CRRT.

CRRT can significantly reduce the formation of intestinal wall edema resulting from systemic inflammatory response syndrome and sepsis/septic shock. The effects of CRRT on fluid balance can help in early initiation (up to 48 hours) of enteral nutrition, which is recommended in the guidelines of many scientific societies (i.e., European Society for Nutrition and Metabolism [ESPEN], American Society for Parenteral and Enteral Nutrition [ASPEN], and International Symposium on Intensive Care and Emergency Medicine [ISICEM]).

Quantifying nitrogen balance is not feasible during CRRT. Amino acids are molecules of relatively low MW, ranging from 89 Da for alanine to 214 Da for tryptophan. Therefore, the loss of amino acids during CRRT procedures is substantial. A study by Scheinkestel et al. has shown that during CVVHD, 17% of amino acids administered intravenously are lost on average (range, 13%–24%).[61] Protein delivery should hence be increased by 25% to compensate for losses in the effluent. Bellomo et al. suggested an amino acid supply of up to 2.5 g/kg/day to ensure a positive nitrogen balance in these highly catabolic patients. The addition of glutamine (alanyl-glutamine dipeptide 0.3–0.6 g/kg/day) to TPN, especially during CRRT, is recommended by the ESPEN (Singer 2009).

AKI is associated with increased triglyceride content of low-density lipoproteins, altered lipolysis, and reduced

hepatic lipase activity. The resulting impairment in lipid metabolism may cause up to a 50% decrease of lipid, and especially triglyceride clearance[62] (Leverve 2010). This enhances the risk of hyperglycemia, particularly in parenterally fed patients. Lipids may also become involved in the early packing or clotting of filters when unfractionated heparin is used as an anticoagulant. This is seen less with citrate.[63]

The nutritional impact of nonintentional calories delivered as citrate, lactate, and glucose during CRRT must be considered. Euglycemia should be the goal.

Electrolyte disturbances are frequently present and should be treated accordingly. Hypokalemia is present in 5%–25% of patients treated with CRRT[64] (Palewsky et al. 2008, Bellomo et al. 2009) and is mainly due to inadequate potassium supplementation. Hypocalcemia is relatively common during CRRT and has sometimes been noted in up to 50% of patients (Honoré 2013). According to a 2016 meta-analysis, hypocalcemia was more common in cases of citrate-based anticoagulation.[65] The incidence of hypophosphatemia during CRRT is high and ranges from 10.9% to 65% (Honoré et al. 2013). Hypophosphatemia has been associated with failure to wean from mechanical ventilation in medical ICU patients.[66] Frequent (every 6–8 hours) assessment of serum electrolytes and acid-base status is needed to correct electrolyte losses, modify electrolyte content of CRRT or intravenous solutions, and adapt oral supplementation.[67,68]

Vitamins B_1, B_6, B_9, and C are lost in the effluent and should be adapted to the effluent dose. Trace elements, except for selenium, are not cleared in relevant quantities. Manganese accumulation, although rare, is of concern because of potential neurotoxicity.

Outcome Data

In children with AKI who require CRRT, the presence of sepsis, multiple organ dysfunction syndrome (MODS), and FO greater than 20% at the time of CRRT initiation are significantly associated with higher mortality. In addition, the duration of mechanical ventilation, PICU stay, hospitalization, and time to renal recovery were all significantly prolonged for survivors who had FO greater than 20%.[6]

A multicenter pediatric ECMO cohort study demonstrated that severe FO was very common at CRRT initiation. They also found an independent association between the degree of FO at CRRT initiation with adverse outcomes, including mortality and increased duration of ECMO support. The results suggest that intervening prior to the development of significant FO may be a clinical therapeutic target and warrants further evaluation.[12,69]

Single-center studies identify outcomes by disease and modality.[19,30,70–74] Fleming et al. demonstrated that the use of CRRT was superior to PD in the pediatric postoperative cardiac population, with improved clearance and nutritional delivery. Due to small numbers, survival could not be adequately addressed.[75] Smoyer et al. identified the use of pressors as a negative factor in survival during pediatric CRRT.[16] In addition, patients undergoing both convective and diffusive clearance fared better than those with convective clearance only. In a particularly well-performed investigation, Goldstein et al. demonstrated that accumulated FO (%FO = ((Fluid In − Fluid Out)/PICU admission weight)) × 100%) in children at the time of CRRT initiation had a significant negative impact upon the outcome, with survivors having an average fluid accumulation of 16% and nonsurvivors having an average fluid accumulation of 34%.[71] The pediatric risk of mortality score (PRISM) score did not appear to correlate with the outcome. Further, Goldstein et al.,[27] using the ppCRRT Registry Group, evaluated 116 children from seven separate centers with multiple organ dysfunction syndromes. Patient survival was inversely correlated with percent FO at the time of initiation of CRRT ($p < 0.05$), including controlling for severity of illness using the PRISMA 2 score. Survivors had a mean FO of 14.2%, while nonsurvivors had a mean 25.4% FO. The overall survival rate was 52% in this cohort. Gillespie et al.[76] and Foland et al.[77] provide further support that lower %FO at the time of starting CRRT in pediatric patients correlates with improved survival. The underlying disease process and the use of vasopressor agents are negative and significant factors predicting outcome, as demonstrated in a large cohort of children with AKI treated by PD, HD, or CRRT.[19] Zobel et al.,[78,79] through some pioneering work in infant CRRT, demonstrated that CVVH[D] in neonates has more effective urea clearance than CAVH[D]. Symons et al.[80] showed that 86 infants between 3 and 10 kg requiring CVVH[D] had a difference in survival when compared to the older children.

Many leaders in the field of CRRT still view that the outcome of children with AKI is related to the overall severity of illness, and the current scoring systems (APACHE, PRISM) do not adequately capture or predict the multitude of confounding variables that occur in this population. Utilization of the modified KDIGO criteria describes clinically relevant AKI in neonates and infants after cardiac surgery and provides more important subsequent postoperative outcomes.[81] Cardiac surgery-related AKI based on n-KDIGO criteria is common in neonates and is closely associated with higher mortality, especially in patients with severe cardiac surgery related-AKI (CS-AKI).[82]

PICU mortality of pediatric cancer and hematopoietic stem cell transplant patients requiring CRRT remains quite high.[83]

Special Applications of Continuous Renal Replacement Therapy

Extracorporeal Membrane Oxygenation and Continuous Renal Replacement Therapy

Cardiopulmonary failure in the PICU or neonatal ICU (NICU) leads to multiorgan dysfunction and AKI that may

necessitate their requirement of ECMO. Approximately 50% of these children undergo CRRT for AKI at some time during their course of ECMO[84,85] (Smith et al. 2009). The ECMO circuit provides access, anticoagulation (heparinization), and a blood flow rate generally in excess of 100 mL/kg/min. It is imperative that the hemofilter not be placed in series with the oxygenator. Parallel placement of the hemofilter may cause blood to bypass the oxygenator in favor of the lower resistance circuit of the hemofilter, causing it to rupture and thereby decreasing oxygen to the circuit. The hemofilter blood flow rate may be 200–300 mL/min. In a small child, this may result in excessive clearance over 100 mL/min and will impact adequate nutrition and pharmacological dosing. The optimal position is to "pull" post oxygenator and return to the bladder of the ECMO circuit. In larger children, these post-oxygenator blood flow rates may not allow acceptable clearance. In these cases, replacement of the smaller surface hemofilter with a larger surface dialyzer may overcome these issues. Some centers are placing the CRRT machine in series with the ECMO circuit. This has the advantage of less clearance of medications and nutrition along with better control of the UF rate with the newer machines.

FO is the most common indication for initiation of CRRT while on ECMO. A multicenter pediatric ECMO cohort study demonstrated that severe FO was very common at CRRT initiation and found an independent association between the degree of FO at CRRT initiation with adverse outcomes, including mortality (20% in survivors vs. 30% in nonsurvivors) and increased duration of ECMO support.[12]

Extracorporeal Life Support Organization (ELSO) guidelines now recommend minimizing the degree of FO and trying to maintain euvolemia (http://www.elso.med.umich.edu/Guidelines.html).

Concurrent use of CRRT and ECMO can be performed by incorporation of either an in-line hemofilter or a CRRT machine into the ECMO circuit.[86] With either type of circuit, return blood from the renal replacement machine should be connected before the oxygenator so that any air or clot will be trapped in the oxygenator and not sent to the patient (Fig. 82.2A, B).

Additional heparinization is not necessary if patient is adequately heparinized for ECMO. If anticoagulation is contraindicated for some reason, then citrate anticoagulation can be used as an alternative.

The access pressure alarms present in CRRT machines have set limits based on the individual CRRT device. The default access pressure alarms are typically negative. However, when these machines are operated in series with ECMO, the positive pressure at the entry point of the CRRT machine will create pressures close to zero or positive. These pressures can lie outside the default pressures of the machine, and thus, the alarm settings may have to be changed when using CRRT on ECMO. Some machines (including the Gambro Prismaflex) give the clinician the ability to adjust alarm settings. Other machines (including the NxStage System One, the Fresenius 2008K, and the older Gambro Prisma) do not have these capabilities. If the machines are not able to change the default access pressure, flow restrictors placed on the outside of the tubing have been used to keep the pressures within the pressure alarm limits. These clamps are not recommended because they portend added risk of hemolysis and thrombosis.[86]

Inborn Errors of Metabolism

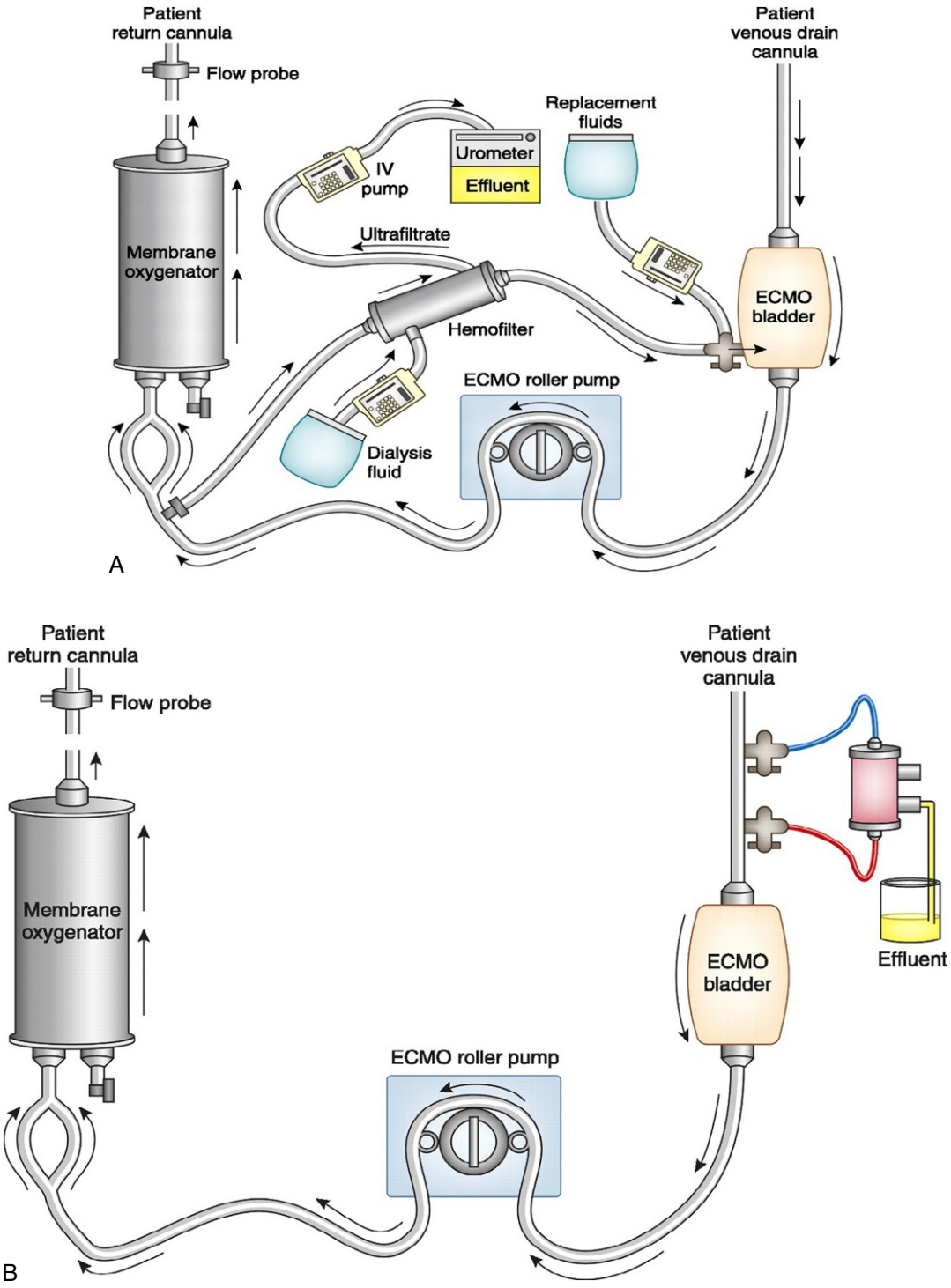
Along with appropriate clinical examination and correction of dehydration that may accompany metabolic disorders, the utilization of CRRT for treatment of inborn errors of metabolism (such as urea cycle defects; Fig. 82.3) has become standard practice.

Hyperammonemia—Etiology and Flow Diagram

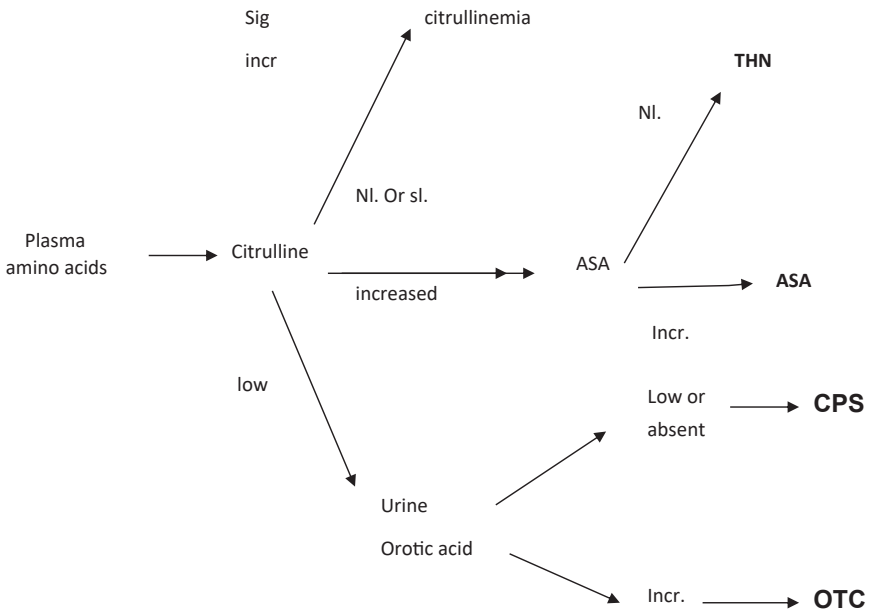
- **Urea cycle defects**
  - Carbamyl phosphate synthetase (CPS)
  - N-acetylglutamate synthetase
  - Ornithine transcarbamylase (OTC)
  - Argininosuccinate synthetase (ASA)
  - Argininosuccinate lyase (AL)
  - Arginase
- **Transient hyperammonemia of the newborn (THN)**

Flow Diagram to Evaluate Hyperammonemia

CRRT is an efficient adjuvant therapy for the acute treatment of inborn errors of metabolism. Both ammonia, which is elevated in urea cycle defects and some organic acidemias, and branched-chain amino acids, which are elevated in maple syrup urine disease, are effectively cleared.[87–90] Because CRRT has a creatinine clearance of 15–50 mL/min compared to that achieved with IHD of >100 mL/min, initial treatment of severe hyperammonemia (>1000 mcg/dL) should be HD, with transition to CRRT once serum ammonia is under 200 mcg/dL (Clark and Ronco 2000). The combined use of HD and CRRT results in improved control of hyperammonemia and prevents the rebound of serum ammonia levels seen with intermittent therapy (McBryde, Brophy, Gregory, Maxvold, Gardner, Mottes, Bunchman 2001). In patients with less severe hyperammonemia, CRRT alone can be used as initial therapy. Because the goal of CRRT in patients with metabolic diseases is the rapid removal of toxic metabolites such as ammonia, the CRRT prescription should be altered to maximize clearance of these molecules. Blood flow rate should be increased to 7–10 mL/kg/min, where possible, and dialysate flow rate increased to 4000 mL/1.73 m^2. With these increased flow rates, care must be taken so that patients do not develop hypophosphatemia. We routinely use a phosphate-containing dialysate on all patients with inborn errors of metabolism receiving RRT. The number of cardiovascular complications occurring in this population decreased substantially following the initiation of this practice (unpublished data). In addition, patients with inborn errors of metabolism and severe



• **Fig. 82.2** (A) Renal replacement therapy using an in-line hemofilter during extracorporeal membrane oxygenation (*ECMO*). As blood comes from the patient via the venous drain cannula, it goes through the ECMO bladder to the ECMO pump, to the membrane oxygenator, and back to the patient via a return cannula. Blood is shunted from the circuit to the in-line hemofilter and returned to the ECMO pump. Fluid (ultrafiltrate) can be controlled using an intravenous (*IV*) pump. Replacement or dialysis fluid can be used for solute clearance and/or to achieve metabolic control. (B) Renal replacement therapy (RRT) using an RRT machine during ECMO. If the ECMO circuit uses a roller pump, a proportion of the circuit blood comes from the patient via the venous drain cannula and enters the RRT machine, where replacement, dialysis, and ultrafiltration occur. Blood from the RRT machine then goes back to the ECMO bladder to the ECMO pump, the membrane oxygenator, and back to the patient via a return cannula. If a centrifugal pump is used, the RRT machine must be connected after the ECMO bladder to prevent air entrapment.



• **Fig. 82.3** Flow diagram to evaluate hyperammonemia. *ASA*, Argininosuccinate synthetase; *CPS*, carbamyl phosphate synthetase; *OTC*, ornithine transcarbamylase; *THN*, transient hyperammonemia of the newborn.

hyperammonemia are often infants, and the combination of their small size and the increased blood flow rates needed for adequate ammonia clearance leads to a high risk for hypothermia. Preventative measures such as heat lamps, warming blankets, warming of the circuit tubing, and/or the use of an in-line blood warmer need to be taken with the initiation of CRRT. In addition to HD and/or CRRT, appropriate pharmacologic therapy needs to be initiated as soon as possible so that the primary disease can be controlled. However, CRRT has been shown to clear components important in alternative pathways of ammonia excretion, such as glutamine and glycine (McBryde, Kershaw, Kudelka, Smoyer, Gardner, Brophy 2002). It is also likely, given the molecular size of the pharmacologic agents used to treat metabolic disorders, that there is substantial clearance of these therapies, and the administration of increased doses of these agents should be considered. Unlike nutritional supplementation that is required in AKI, the treatment of inborn errors of metabolism often requires that protein be significantly restricted. This necessitates that the clinician focuses on the dialysate/filter replacement fluid composition in order to provide homeostatic electrolytes, along with the fact that many of these children have otherwise normal renal function.

Infant Dialysis Machines

Neonatal AKI is an underrecognized morbidity of neonates. Its incidence remains unclear; however, reported numbers in NICUs range between 8% and 40% and are associated with a high mortality (25%–50%)[91] (Ronco 2014).

Special considerations and issues related to infant or neonatal CRRT include the following: small patients with small blood volume, equipment designed for bigger people, no specific protocols, complications may be magnified, no clear guidelines, limited outcome data, volume-related problems, biochemical and nutritional problems, hemorrhage, infection, thermic loss, and technical and logistical problems.

Factors affecting the performance of CRRT in infants and neonates are patient size, vascular access, hemodynamic stability, institutional expertise, and hardware and modality issues.

Epidemiology and management of AKI in pediatric patients have changed significantly. In the 1980s, the leading causes were primary kidney disease, hemolytic uremic syndrome, acute tubular necrosis, and burns. Currently, the most common etiologies include cardiac surgery and effects of cardiopulmonary bypass, perinatal accidents, bone marrow transplant, MODS, sepsis, and septic shock.

Three different CRRT machines, Aquadex, Carpediem, and NIDUS, have been developed for neonatal use. Carpediem and Aquadex are currently FDA approved for use in the United States.

Aquadex

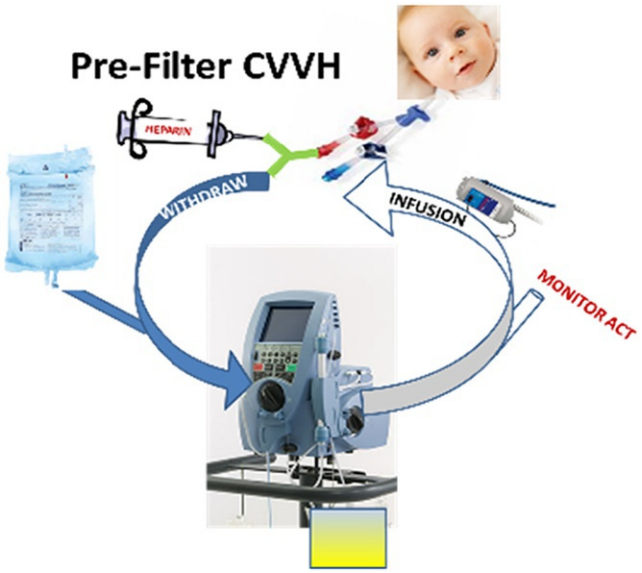
This machine was pioneered by Askenazi et al. from the University of Alabama and was FDA approved for UF in 2007. In their experience with 12 patients, 5 patients in the cardiac ICU (CICU) and 7 in the neonatal NICU (9 for AKI and 3 for severe congenital CKD), with a median age at initiation of 30 days (interquartile range [IQR], 13–38 days), median weight at initiation was 3.4 kg (IQR, 3.0–4.3 kg). The median duration was 14.5 days (IQR, 10–22.8 days). Access was obtained via a double-lumen vascular access, and single lumen catheters in three with congenital heart disease had two single lumen catheters. A total of 101 circuits were utilized over a period of 261 days. There were 12 new starts and 89 restarts. Fifty-nine (61%) circuits lasted 72 hours; 80% had blood prime with $NaHCO_3$ + CaCl, and 20%

had saline prime. Close to half of the patients survived to discharge. Complications included transient hemodynamic instability, hypothermia, minor bleeding in a quarter of the patients, and right atrial thrombus in one patient.

The Aquadex circuit (Baxter Corporation, Minneapolis, MN) has a 33 mL volume when using the UF 500 filter set with the HCT monitor. Use of a roller pump provides negative pressure through the access line to bring blood from the patient to the hemofilter. A second pump provides negative pressure on the hemofilter to remove plasma volume. The filter is 0.12 m^2 and is made of polysulfone membranes. The SCs for urea, creatinine, vitamin B_{12}, and albumin are 0.98, 0.98, 0.98, and <0.02, respectively. Blood is returned via an inlet (return) line to the patient. The circuit has an in-line continuous HCT sensor, and there is software in place to automatically stop removing fluid if the HCT hits the prescribed HCT limit. The tubing set has pigtails before and after the filter. The blood pump can run at 10 to 40 mL/min (at intervals of 5) and has an accuracy of +15%−20% of setting for withdraw pressure of 250 mm Hg. The UF pump has a range of 0 to 500 mL/h in 10-mL/h increments and an accuracy of ±10% of setting. The machine has an air detector and a blood leak detector. The operational range for the access (withdraw), return (infusion), and UF (transmembrane) pressures is −350 to 500 mm Hg. UF rates of up to 500 mL/h are ample for clearance of waste products in small children in the CVVH mode; no port is present to provide countercurrent dialysis (Aquadex Flex Flow user guide).

Venous access is placed by the surgical or intensive care team in consultation with the pediatric nephrologist. Blood flow rate is titrated to 40 mL/min. A y-connector is placed on the withdraw (access) line to provide continuous heparin for anticoagulation. Prefilter replacement fluid is infused with an Alaris (head unit model #8015; large volume pump module #8100) fluid infusion system via the proximal pigtail of the circuit. Anticoagulation monitoring is obtained from the distal pigtail of the circuit. Heparin infusion rate is titrated to ACT goals specified by the team. Target ACT is set at 180–220 seconds and afterward reduced to 160–180 seconds. UF rates are adjusted to match the intake of the previous hour, in addition to the prescribed amount to "leave on" or "take off." A blood warmer (AstoFlo Plus Stihler Electronic, Stuttgart, Germany) is placed on the infusion (return) line of the circuit. The HCT limit is set to 50%. Circuits run continuously and must be changed out every 72 hours.[92]

Circuits are primed with packed red blood cells (pRBCs) or saline according to our institution's guidelines. Therefore, in accordance with institutional protocols, if a patient had <10% of extracellular volume (ECV) and was clinically stable, a saline prime was used, while if a patient had an ECV ≥10%, the circuit was primed with pRBCs. The blood prime is diluted 1:1 with sodium bicarbonate (to correct low pH and decrease HCT), and 1 mL of 10% calcium gluconate is infused into the patient (to compensate for the low ionized calcium level of banked blood) (Bridges et al. 2012), to get the pRBC close to physiologic. If criteria for blood prime are met, and the circuit runs for 72 hours, or a planned circuit change occurs, we cross primed the new circuit with the blood of the expiring circuit, according to institutional protocols (Fig. 82.4).



• **Fig. 82.4** Aquadex machine. (Adapted from Askenazi D, Ingram D, White S, et al. Smaller circuits for smaller patients: improving renal support therapy with Aquadex™. *Pediatr Nephrol.* 2016;31(5):853–860, with permission.)

NIDUS

The NIDUS provides HD to infants as small as 800 g (range 800 g–8 kg). It is a syringe-driven machine that withdraws a small amount of blood (5–12.5 mL), passes it through a dialysis filter, then returns it to the patient. The circuit volume is less than 10 mL and requires no blood prime. UF rates in the range of 0–60 mL/h can be achieved with microliter precision of UF control. Treatment can be performed using a single lumen central venous line for up to 24 hours at a time.

Carpediem

The Carpediem was originally designed to perform only CVVH in newborns and infants weighing less than 10 kg. It is a miniaturized CRRT machine developed in Italy in 2014 for neonates and small infants with reduced priming volumes and the capacity to accurately handle very low blood flow in order to maintain prescribed UF.

Operational characteristics include a blood flow of 0–50 mL/min, UF of 0–5 mL/min, the accuracy of 0.1 mL/min, and a priming volume of 27 mL only.

The Carpediem has been FDA approved (2020) for use in 3–10-kg patients and is beginning to be placed at some of the larger children's hospitals in the United States.

Conclusion

CRRT affords the critically ill pediatric patient an efficient, reliable, and safe form of RRT. CRRT use is expanding within the pediatric community as the availability of this technology becomes mainstream and adapted to the pediatric patient.

As the virtues of early intervention with these modalities are further recognized, so too will the role of CRRT be delineated and refined in order to serve best the clinicians who use it. With the ever-increasing use of ECMO in neonates and children, especially after cardiopulmonary bypass, the combination of CRRT is crucial, and its early use improves mortality and morbidity. Miniaturized infant dialysis machines like the Aquadex in the United States continue to evolve. The continued cooperation among industry, nursing, nephrologists, intensivists, and other medical professionals is mandatory for pediatric CRRT to continue to be successful.

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Prevention and Treatment of Bone Disease in Pediatric Dialysis Patients

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Childhood and adolescence are crucial times for developing a healthy skeletal system; alterations in bone modeling/remodeling in youth carry consequences that severely impact quality of life even into adulthood.[1] In childhood, chronic kidney disease (CKD) causes disordered regulation of mineral metabolism, with subsequent alterations in bone modeling, remodeling, and growth. Additionally, uremia itself, independent of altered mineral metabolism, impairs bone cell function in a manner that contributes to bone disease.[2] CKD-mediated alterations in bone structure, strength, and growth are termed "renal osteodystrophy" (ROD). Due to the link between bone disease, abnormal mineral metabolism, and cardiovascular disease in uremic patients, ROD is one part of the systemic disorder that is termed the "CKD–mineral and bone disorder" (CKD-MBD).[3]

This chapter first describes the clinical manifestations of ROD. Pathologic changes at the level of bone are also described. The pathogenesis of secondary hyperparathyroidism and the effects of uremia on bone cell biology are discussed, followed by the biomarkers of bone disease and current treatments for secondary hyperparathyroidism and ROD.

Clinical Features of Renal Osteodystrophy

Growth Failure

Growth retardation is the hallmark of CKD in children. Growth failure is present in children with even mild CKD and worsens as renal function declines. Despite optimal control of bone disease and the availability of recombinant human growth hormone (rhGH), the average height of children starting dialysis is 1.5 standard deviation scores below normal. Growth worsens in dialysis patients, and by transplantation, height is 1.7 SD below that in healthy children.[4] Boys, younger patients, and those with prior renal transplants are at greatest risk for growth failure.[5] Acidosis,[6] anemia, calcitriol deficiency, secondary hyperparathyroidism, and bone deformities all contribute to growth retardation. Overtreatment of secondary hyperparathyroidism with large, intermittent doses of calcitriol and calcium-based phosphate binders may cause adynamic bone disease, which is associated with decreased linear bone growth, despite sometimes elevated serum parathyroid hormone (PTH) levels.[7] Resistance to the actions of growth hormone (GH) also contributes to impaired linear growth in renal failure.[8] Growth velocity increases during rhGH therapy as bioavailability of insulin-like growth factor 1 (IGF1) increases to target tissues.

Due to a variety of factors, a significant proportion of dialyzed children who are candidates for GH therapy do not receive it.[9] Although children who are treated with maintenance dialysis respond less well to rhGH therapy than do children with less severe CKD, this resistance should not prevent these children from receiving rhGH. Current recommendations suggest that children on dialysis who have growth potential should receive rhGH if they have persistent growth failure, defined as a height below the third percentile for age and sex and a height velocity below the 25th percentile, once other potentially treatable risk factors for growth failure have been adequately addressed.[10]

Deformities and Bone Fragility

Decreased bone strength is a clinical feature of CKD-MBD that afflicts children even in early CKD stages. In a prospective cohort of children with CKD, fracture rates were 2 to 3 times those observed in the general population. Advanced pubertal stage, taller height, and higher PTH levels were associated with increased fracture risk, suggesting that the combination of high turnover osteodystrophy and pubertal growth increases bone fragility in the pediatric CKD population; interestingly, the use of phosphate binders (mainly calcium based) was protective. However, it is also important to note that as many as 20% of this population had mild (stages 1 and 2) CKD, suggesting that bone fragility contributes to morbidity in children at all CKD stages.[11] Bone deformities are also common. Genu valgum is the most common skeletal deformity in pubescent and adolescent CKD patients, while young children may exhibit exaggeration of the physiologic varus alignment. Radiographic features associated with rickets, such as metaphyseal widening

of the wrist and ankle, craniotabes, and rachitic rosary, may occur. Pathologic or stress fractures may arise if the bones remain bowed and weak.[1]

Pathology of Renal Osteodystrophy: Abnormalities in Bone Turnover, Mineralization, and Volume

Renal bone disease (ROD) is nearly universal in children starting dialysis. Traditionally, ROD has been defined by changes in trabecular bone turnover, ranging from high bone turnover (osteitis fibrosa) to lesions of low bone turnover (adynamic bone disease and osteomalacia). However, alterations in skeletal mineralization and volume are also common in pediatric dialysis patients[12] and may contribute to outcomes such as fractures, skeletal deformities, and poor growth, which persist despite normalization of bone turnover.[1] Even though it is rarely available in daily clinical practice, bone histomorphometry remains the gold standard for the diagnosis of ROD.[13]

Turnover

Abnormalities in bone turnover—both excessively low and excessively high—are prevalent in pediatric CKD patients. High bone turnover is the most common lesion in children treated with maintenance dialysis.[12] Excessive PTH concentrations result in increased bone matrix resorption with concomitant release of minerals into the circulation. Prolonged exposure to elevated PTH levels and increased bone turnover may lead to fibrous changes in bones; thus, the ROD associated with prolonged secondary hyperparathyroidism is often termed "osteitis fibrosa cystica."[14]

A state of low-turnover bone disease (adynamic ROD), defined as decreased bone formation rate in conjunction with decreased cellular activity and an absence of excessive osteoid accumulation, is most common in adult dialysis patients but may also occur in children treated with overaggressive active vitamin D sterols and calcium salt therapy. In addition to the increased risk that is also observed in adults with low bone turnover, adynamic bone disease in children treated with dialysis is associated with exacerbated growth failure.[15,16]

Mineralization

Alterations in skeletal mineralization, defined by increased accumulation of unmineralized bone (osteoid) in conjunction with delayed rates of mineral deposition, are prevalent in children with CKD.[17,18] Defective mineralization that is associated with low to normal bone turnover is termed "rickets" in growing children, and its histomorphometric characteristics include wide osteoid seams, increased numbers of osteoid lamellae, increased percentage of trabecular surface covered with osteoid, and a diminished rate of mineralization or bone formation, as assessed by double tetracycline labeling. Fibrosis is typically absent.[13] Defective mineralization in combination with increased bone formation rates is termed "mixed uremic osteodystrophy" and is characterized by wide osteoid seams, prolonged mineralization times, bone marrow fibrosis, and increased bone formation rates.[12]

Volume

Because PTH is anabolic at the level of trabecular bone, high levels of serum PTH are typically associated with increases in bone volume, trabecular volume, and trabecular width. Low bone volume is rare in the pediatric CKD population.[12]

Circulating Factors Contributing to Renal Osteodystrophy

With the exception of a few well-defined monogenetic disorders, such as cystinosis,[19] oxalosis,[20] and autosomal dominant polycystic kidney disease,[21] which have direct deleterious effects on the skeleton, the pathologic features of ROD are remarkably similar in children with end-stage kidney disease (ESKD) regardless of the underlying disease.[22] This suggests that the uremic milieu itself, rather than underlying genetics, contributes to the majority of the ROD phenotype in this population.

While not all the factors contributing to bone disease in this population are known, disturbance in mineral ion homeostasis has been well characterized. More recent data suggest that uremic toxins themselves also influence bone cell biology, contributing to important features of bone disease.[2]

Calcium and Phosphorus

Since childhood and adolescence are critical times for developing a healthy skeleton, with the skeletal calcium content increasing from 25 g at birth to 1000 g in adulthood, hypocalcemia directly results in decreased volumetric bone mineral density (BMD) scores in growing children.[23] By contrast, hypercalcemia oversuppresses PTH secretion, thus, leading to low bone turnover (adynamic bone disease).[15,16] While hyperphosphatemia drives secondary hyperparathyroidism (as earlier), phosphate depletion may play a major role in the development of rickets/osteomalacia in patients treated with frequent (daily) dialysis and/or with inadequate nutrition.[24]

Acidosis

Not only is chronic acidosis is a risk factor for more rapid CKD progression in children,[25] but also, it is associated with poor skeletal mineralization as free hydrogen ions directly release calcium from bone.[26] In addition, acidemia stimulates osteoclast differentiation and osteoclast-mediated bone resorption[27,28] and inhibits osteoblastic-driven

mineralization. Thus untreated acidosis likely contributes to the high prevalence of skeletal mineralization observed in dialyzed children.[12]

Parathyroid Hormone

PTH directly increases the cellular activity of osteoblasts and, indirectly, osteoclast activity[29–31]; thus, excess circulating PTH levels (hyperparathyroidism) is a major contributor to increased bone turnover in CKD. PTH also affects osteoblast commitment,[32] as well as osteoblast and osteocyte maturation.[33] High PTH levels, thus, contribute to excessive osteoid accumulation and defective bone mineralization in children with advanced CKD.[18]

Fibroblast Growth Factor 23

Both underexpression and overexpression of fibroblast growth factor 23 (FGF23) contribute to rickets/osteomalacia in mice and humans with normal kidney function; whether this is a direct effect of FGF23 on mineralization and osteoclastic differentiation/resorption activity[34] or an indirect effect—through altered circulating phosphate and 1,25$(OH)_2$vitamin D concentrations—remains unclear.[35–39]

Uremic Toxins

Alterations in osteoblast and osteocyte biology that are unrelated to alterations in mineral metabolism develop early in the course of CKD. The uremic milieu consists of a myriad of metabolic by-products that are not cleared in the context of kidney failure. One such compound, indoxyl sulfate, is directly toxic to the bone.[40] CKD bone is characterized by a marked delay of osteocyte maturation in vivo and osteoblast maturation in vitro[2]; these defects are partly a result of secondary hyperparathyroidism[33] but also reflect changes from chronic exposure to uremic toxins.[2]

Pathogenesis of Skeletal Disease in Chronic Kidney Disease

Abnormal mineral ion (i.e., calcium and phosphorus) homeostasis and dysregulated hormone (i.e., PTH, vitamin D, and FGF23) expression contribute substantially to the development of ROD. These factors are thus biomarkers of bone disease and also therapeutic targets.

The Pathogenesis of Secondary Hyperparathyroidism

In early (stage 2) CKD, increased production of the osteocyte-specific hormone FGF23,[41] decreased renal FGF23 degradation,[42] and decreased renal FGF23 clearance[43] all contribute to a rise in circulating FGF23. Increased circulating FGF23 levels promote renal phosphate excretion in the face of declining kidney function,[44] thus maintaining circulating phosphate concentrations in the normal range, and also suppresses PTH expression,[45] helping to maintain serum PTH levels in the normal range until 50% of kidney function is gone. However, rising FGF23 concentrations also suppress renal 1α-hydroxylase activity,[44] thus suppressing the production and enhancing the metabolism of 1,25$(OH)_2$D (calcitriol), the biologically active form of vitamin D. A steady decline in circulating 1,25$(OH)_2$D concentrations, in turn, contributes to secondary hyperparathyroidism and parathyroid gland hyperplasia by decreasing intestinal calcium absorption[46,47] and by decreasing the expression of the vitamin D and calcium-sensing receptors (*VDR* and *CASR*) in the parathyroid glands.[48,49] Low calcitriol levels thus allow parathyroid cells to proliferate, contributing to autonomous PTH secretion in dialysis patients.

Due to limited dietary intake, often limited sunlight exposure, and decreased dermal synthesis of vitamin D_3 in response to sunlight,[50,51] 25(OH)vitamin D (25(OH)D) deficiency is also prevalent in patients with CKD. Low levels of 25(OH)D contribute to the development of secondary hyperparathyroidism, both directly and through limiting substrate for the formation of 1,25$(OH)_2$D and indirectly by suppressing PTH through the internal production of the parathyroid gland–specific 1α-hydroxylase.[52–56] Supplementation with ergocalciferol has been shown to decrease serum PTH levels and to delay the development of secondary hyperparathyroidism in pediatric patients with CKD.[56]

Hypocalcemia is a potent—in fact, the primary—stimulus for PTH release. Low circulating calcitriol levels result in low intestinal calcium absorption in late CKD stages.[57] Phosphorus retention also contributes to the pathogenesis of secondary hyperparathyroidism in dialysis patients. Hyperphosphatemia lowers blood ionized calcium, impairs 1α-hydroxylase activity, thereby, preventing the conversion of 25(OH)D to 1,25$(OH)_2D_3$,[58] and directly promotes PTH and FGF23 secretion.[59] Phosphorus also increases the stability of the PTH mRNA transcript.[60]

Prediction of Skeletal Health

No one specific biomarker is sufficient to diagnose and treat the bone lesions associated with CKD reliably. Mineral ions, including calcium and phosphorus, are essential components of bone structure and strength, but circulating levels of these ions comprise less than 0.1% of total body calcium and phosphorus stores. Thus assessments of serum calcium and phosphorus are incomplete predictors of bone health. Assessments of the hormones that regulate their absorption and excretion—such as PTH, vitamin D, and FGF23—add to the assessment of bone health but are also imperfect predictors. Due to the interplay between mineral ions and hormones, circulating values may fluctuate from month to month, and the global management of CKD-MBD must consider serial

assessments of mineral ions and hormones.[3] Predictive algorithms demonstrate that a combination of serum calcium, alkaline phosphatase, and PTH levels may lead to a more precise noninvasive assessment of turnover and mineralization abnormalities in the pediatric CKD population than any one parameter alone[12]; thus, treatment should be based on values of mineral ions and hormones considered in the context of one another and on trends of these different markers over time.[3]

Calcium and Phosphorus

Hypocalcemia is a classic feature of untreated CKD, occurring in response to decreased intestinal calcium absorption in the face of declining 1,25(OH)$_2$vitamin D concentrations.[57] Calcimimetic agents, which allosterically activate the calcium-sensing receptor on the parathyroid gland, may also contribute to hypocalcemia in long-standing dialysis patients during treatment.[61] By contrast, long-term treatment with high doses of calcium-based phosphate binders, vitamin D sterols, and dialysates with high calcium concentration may contribute to hypercalcemia.[62] Since hypocalcemia and hypercalcemia both contribute to low bone mass and adynamic bone disease, respectively,[15,16] serum calcium levels should be maintained in age-appropriate normal ranges in dialyzed children,[3] and adequate calcium intake should be provided, taking into account nutrition, supplements, calcium-based binders, and calcium in the dialysate.

Adequate phosphate nutrition is critical for bone mass and is also important for many cellular processes, including ATP production. Higher concentrations of phosphate are associated with mortality among adult patients with all CKD stages,[63] but chronic hypophosphatemia may also cause cardiac dysfunction and/or bone hypomineralization (rickets/osteomalacia),[24] both of which may lead to long-term health consequences in growing children. Thus as with serum calcium, serum phosphate levels should be maintained in the normal range for age in children with CKD,[3] and serum calcium and phosphorus concentrations should be measured q1–3 months in children treated with maintenance dialysis[3] (Table 83.1).

Alkaline Phosphatase

Tissue nonspecific alkaline phosphatase has been used for many years as a predictor of bone turnover in CKD patients. Alkaline phosphatase is made by osteoblasts; high levels occur in the context of increased osteoblastic activity as occurs in high bone turnover or impaired osteoid mineralization. Alkaline phosphatase demonstrates a lower variability and may thus be better suited for the diagnosis and longitudinal follow-up of bone turnover. Current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines suggest that alkaline phosphatase be measured yearly in dialyzed children or more frequently if PTH is elevated.[3]

Parathyroid Hormone

As CKD progresses, the skeleton becomes resistant to the calcemic effect of PTH.[64,65] This resistance may also contribute to secondary hyperparathyroidism. Amino-terminally truncated PTH fragments, such as PTH,$^{7-84}$ antagonize the calcemic actions of the full-length PTH molecule.[66,67] Dialysis patients with increased circulating levels of the full-length PTH molecule also have increased circulating levels of the amino-terminally truncated fragment PTH$^{7-84}$ and are resistant to the calcemic actions of PTH in vivo.[65] A wide variation in PTH assays has been reported between manufacturers, complicating the interpretation of PTH values still further.

Optimal levels of PTH in CKD patients are controversial[68,69]; values between 2 and 9 times the range for individuals with normal renal function have been associated with normal bone formation in patients treated with maintenance dialysis.[13] Importantly, treatment should not be based on a single elevated value but taken in the context of previous PTH measures. PTH levels that are persistently elevated or progressively rising warrant examination of modifiable factors, such as vitamin D insufficiency or deficiency, hypocalcemia, and hyperphosphatemia, and marked changes in PTH levels above or below the recommended range should prompt an initiation or change in therapy to avoid progression outside the recommended range. Baseline PTH concentrations should be evaluated in all patients with stage 3 CKD. PTH values should be followed every 3–6 months in children with CKD stage 5[3] (Table 83.2).

TABLE 83.1 Normal Ranges for Calcium, Phosphorus, and Alkaline Phosphatase in Children

Age (Years)	Serum Phosphorus (mg/dL)	Serum Total Calcium (mg/dL)	Blood Ionized Calcium (m/M)	Alkaline Phosphates (IU)
0–0.25	4.8–7.4	8.8–11.3	1.22–1.40	
1–5	4.5–6.5	9.4–10.8	1.22–1.32	100–350
6–12	3.6–5.8	9.4–10.3	1.15–1.32	60–450
13–20	2.3–4.5	8.8–10.2	1.12–1.30	40–180

Adapted from KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. *Kidney Int Suppl*. 2009;(113):S1–130. https://doi.org/10.1038/ki.2009.188.

TABLE 83.2 Recommended Frequency for Monitoring Various Biomarkers in Dialyzed Children

	Baseline	Q1–3 months	Q3–6 months	Q12 months
Calcium	x	x		
Phosphorus	x	x		
PTH	x		x	
Alkaline phosphatase	x			x
25(OH)vitamin D	x			

PTH, Parathyroid hormone.
Adapted from KDIGO guidelines, Ketteler M, Block GA, Evenepoel P, et al. Executive summary of the 2017 KDIGO chronic kidney disease–mineral and bone disorder (CKD-MBD) guideline update: what's changed and why it matters. *Kidney Int*. 2017;92:26-36.

Linear Growth

Since growth failure is a hallmark of CKD in children, infants who are treated with maintenance dialysis should have linear growth monitored every 3 months, while older children should be measured at least annually.[3] Notably, bone formation rate increases out of proportion to changes in PTH values during treatment with rhGH, complicating the noninvasive assessment of ROD during therapy[70]; this should be considered when concomitantly treating secondary hyperparathyroidism and growth failure. Bone Mineral Density and Histomorphometry BMD, as measured by dual-energy x-ray absorptiometry (DXA), is not an accurate representation of bone health and is thus not recommended for the evaluation of bone health in children with CKD.[71,72] Computed tomography (CT) provides more accurate assessments of cortical and trabecular bone, and lower cortical BMD, as assessed by peripheral quantitative CT (pQCT), predicts future fracture risk in children with CKD.[73] However, pQCT is not widely available for clinical use. Bone biopsy is the gold standard for the diagnosis of lesions of bone turnover and mineralization and is indicated for the clinical assessment of refractory hypercalcemia, unexplained hypophosphatemia, and unexplained fractures and deformities.[3] However, a bone biopsy is an invasive procedure that is also not widely available for clinical use.[71] Thus, clinical management relies primarily on routine assessments of biomarkers (earlier).

Treatment of CKD-MBD

The aims of CKD-MBD management in children are (1) to maintain blood levels of serum calcium and phosphorus within or near normal limits for age, (2) to maintain serum PTH at levels appropriate for the stage of CKD, (3) to optimize growth, (4) to avoid the development of extraskeletal calcifications, (5) to correct acidosis, denutrition, and anemia, and (6) to prevent or reverse the accumulation of toxic substances such as FGF23, aluminum, and β_2-microglobulin.

Dietary Manipulation of Calcium and Phosphorus

Low serum calcium concentrations contribute to bone disease as well as to impaired nerve and cardiac function, while hyperphosphatemia and hypercalcemia are independent risk factors for vascular calcification and mortality. Patients with untreated CKD commonly ingest as little as 400–700 mg of elemental calcium per day in their diet. Calcium-rich foods such as dairy products tend to be high in phosphorus; thus, increasing dietary consumption of calcium to meet daily needs is accompanied by excessive intake of phosphorus, which cannot be excreted in the face of renal failure.

In industrialized countries, daily phosphate intake varies with age and gender; the typical diet contains 1000 to 1600 mg/day of phosphate. Estimating dietary phosphate intake is complicated by the fact that food composition tables reflect only the phosphate contained in unprocessed foods. Organic phosphates have varying bioavailability based on the source; about 40% to 60% of animal-based phosphate—but somewhat less of plant-based phosphate (20% to 50%)—is absorbed.[3] By contrast, the inorganic phosphate added during food processing, in dietary supplements, and medications are readily absorbed, and inorganic phosphate sources often contain a substantial amount of phosphate that is not included on food tables or labels.[3] Aggressive dietary phosphate restriction is difficult and has the potential to compromise protein intake since phosphorus intake is directly linked to protein intake, with 10–12 mg of phosphorus accompanying each gram of protein. Since adequate protein intake is necessary for growth in children (particularly in children undergoing peritoneal dialysis who have obligate protein losses in the peritoneal dialysate), the intake of fresh and homemade foods should be emphasized over-processed foods in order to curb the disproportionate phosphate burden that is found in food additives. However, protein restriction should be avoided in order to prevent malnutrition in children.[3]

Phosphate-Binding Agents

Phosphate-binding agents reduce intestinal phosphate absorption by forming poorly soluble complexes with phosphorus in the intestinal tract. Calcium-containing salts are used worldwide for the control of hyperphosphatemia and serve as an additional source of supplemental calcium.[74] Several calcium salts, including calcium carbonate, calcium acetate, and calcium citrate, are commercially available. Calcium carbonate is the most commonly used compound; the recommended dose is proportional to the phosphorus content of the meal and is adjusted to achieve acceptable serum levels of calcium and phosphorus. Large doses of calcium carbonate may lead to hypercalcemia, particularly in patients treated concomitantly with active vitamin D sterols or those with adynamic bone,[75] contributing to accelerated vascular calcification and overall mortality. Thus doses of calcium-based binders should be adjusted to maintain normal serum calcium concentrations in children.[3]

Several calcium-free phosphate binders are currently available. Sevelamer is a hydrogel of cross-linked polyallylamine that lowers serum phosphate without inducing hypercalcemia. Sevelamer decreases serum cholesterol and low-density lipoprotein cholesterol while increasing high-density lipoprotein levels[76]; in addition, sevelamer also halts the progression of vascular calcification.[77] These effects may offer additional benefits in reducing cardiovascular complications in patients with end-stage renal disease. Sevelamer carbonate is preferable to sevelamer hydrochloride since the latter may worsen acidosis.

Other alternative phosphate-binding agents include iron, lanthanum, and magnesium compounds. Iron compounds, such as sucroferric oxyhydroxide and ferric citrate, are effective phosphate binders that bolster iron stores and may also decrease circulating FGF23 concentrations.[78] Lanthanum carbonate is a rare-earth element that also effectively controls serum phosphorus and PTH levels without increasing serum calcium values.[79] Magnesium carbonate lowers serum phosphorus levels, but magnesium-free dialysate solutions should be used when these agents are employed.[80] Moreover, large doses result in diarrhea, limiting the use of this compound as a single agent.

Although aluminum-containing phosphate binders are effective, their use should be restricted to the treatment of patients with severe hyperphosphatemia (>7 mg/dL) associated with hypercalcemia in whom other agents are not an option. When used, the dose of aluminum hydroxide should not exceed 30 mg/kg/day, and the lowest possible dose should be given only for a limited period (maximum 4–6 weeks).[81] Plasma aluminum levels should be monitored regularly to avoid encephalopathy and bone disease. Concomitant intake of citrate-containing compounds should be avoided because citrate enhances intestinal aluminum absorption and increases the risk for acute aluminum intoxication.[82]

Intensified Dialysis

Standard prescription peritoneal dialysis and hemodialysis remove far less phosphate (300–400 mg/day for peritoneal dialysis and 800 mg/treatment for hemodialysis) than is ingested on a daily basis; however, intensified dialysis therapy, such as the use of daily, slow, continuous hemodialysis or daily in-home hemodialysis, provides excellent phosphate control. Patients treated with intensified forms of hemodialysis are often able to discontinue phosphate-binding agents; indeed, some patients requiring daily dialysis for other reasons (e.g., reduction of serum oxalate levels in patients with primary hyperoxaluria) develop hypophosphatemia and require the addition of phosphate to their dialysate. Centers that provide daily in-center hemodialysis for children have also reported marked improvements in growth in children treated with daily hemodialysis,[83] making this an attractive modality where available.

Vitamin D Therapy

Despite dietary phosphate restriction, the intake of phosphate-binding agents, and an adequate intake of calcium, progressive secondary hyperparathyroidism causes high-turnover bone disease (osteitis fibrosa cystica) in the majority of young (children and non-diabetic younger adult) patients with advanced kidney disease. Treatment with different forms of vitamin D is an important method for preventing and treating this secondary hyperparathyroidism.

Assessment and Treatment of 25(OH)vitamin D Deficiency

Cutoffs for 25(OH)D deficiency remain controversial. Values below 20 ng/mL are associated with hyperparathyroidism in the general population,[84] and some data suggest that 25(OH)D levels should be maintained over 30 ng/mL.[85] An upper threshold of 48 ng/mL has also been proposed in the European guidelines to avoid toxicity in pediatric CKD.[86] In addition to providing substrate for the generation of $1,25(OH)_2$vitamin D by the kidneys, 25(OH)D directly suppresses PTH secretion by two mechanisms: (1) the parathyroid glands generate $1,25(OH)_2$vitamin D from their own internal 1-alpha hydroxylase activity and (2) 25(OH)D, independent of its conversion to $1,25(OH)_2$vitamin D, directly suppresses the formation of pre-pro-PTH.[56] Current data demonstrate that treatment with ergocalciferol or cholecalciferol to replete 25(OH)D stores forestalls the development of secondary hyperparathyroidism in children with predialysis CKD[55]; thus, 25(OH)D stores should be repleted when deficient.[3]

Active Vitamin D Sterol Therapy

Active vitamin D sterols are analogues of $1,25(OH)_2$vitamin D (calcitriol) that act through a variety of pathways to decrease PTH production. These agents include oral 1α-(OH) D_3 (alfacalcidol), which undergoes 25-hydroxylation in the

liver to form calcitriol, 19-nor-1 a,25$(OH)_2D_2$ (paricalcitol), and 1α-$(OH)D_2$ (1α-D_2, doxercalciferol). The most common lesion of ROD in children continues to be one of high bone turnover due to secondary hyperparathyroidism, and growing children require a positive calcium balance to build a healthy adult skeleton. Daily oral doses of calcitriol have been used to treat symptomatic ROD for decades in this population, diminishing bone pain, improving muscle strength and gait, and resolving the lesions of osteitis fibrosa.[87] Calcitriol also increases intestinal calcium absorption, an important consideration since lower serum calcium levels have been associated with lower cortical bone density in children.[23] Thus, current recommendations suggest that calcitriol and other vitamin D sterols should be used to maintain serum calcium levels within age-appropriate normal ranges in children with CKD.[3,88] Overuse of active vitamin D sterols contributes to hypercalcemia, a risk factor for mortality, and also adynamic bone disease, which is associated with growth failure in children,[15] so overtreatment should be avoided.

Calcimimetics

Calcimimetic agents are allosteric activators of the calcium-sensing receptor. Cinacalcet, an oral medication, is currently approved for use in adult dialysis patients with secondary hyperparathyroidism. Etalcalcetide, an intravenous form of this medication, is also effective in reducing serum PTH concentrations in this population. Although a large prospective trial in 3883 adults with advanced secondary hyperparathyroidism (the EVOLVE trial) failed to demonstrate a beneficial effect of calcimimetics on either cardiovascular events or mortality,[89] cinacalcet use significantly reduced the risk of severe unremitting secondary hyperparathyroidism (defined as serum PTH levels > 1000 pg/mL) together with hypercalcemia (serum calcium > 10.5 mg/dL) in this trial.[89] Studies in children have also demonstrated the efficacy of calcimimetics in treating severe secondary hyperparathyroidism, and cinacalcet can be used in children over 3 years of age on dialysis who have persistent and severe hyperparathyroidism in the presence of high or high-normal calcium levels, despite optimized conventional management, including active vitamin D.[3] The use of calcimimetics in children has been approved in Europe, where usage guidelines have been established,[90] but these agents are not currently approved for use in children in the United States.

Parathyroidectomy

Patients with severe hyperparathyroidism are often unresponsive to vitamin D therapy, developing hypercalcemia and hyperphosphatemia without reduction in PTH values or parathyroid gland size.[91] Calcimimetics are effective in preventing and reducing persistent and severe hyperparathyroidism[61]; however, some CKD patients have severe hyperparathyroidism that fails to respond to medical and pharmacological therapy. These patients are candidates for parathyroidectomy. Clinical features that indicate the need for parathyroidectomy include the presence of hyperplasia and/or hypertrophy of the parathyroid glands (as documented by the presence of biochemical and radiographic features and, if necessary, the findings of osteitis fibrosa cystica on bone biopsy), elevated serum PTH levels unresponsive to vitamin D sterol and calcimimetic therapy, persistent hypercalcemia, pruritus unresponsive to dialysis or other medical treatment, progressive extraskeletal calcification, severe skeletal pain or fractures, and calciphylaxis.[3]

When the decision has been made to perform parathyroid surgery, it is essential to avoid a marked postoperative fall in serum calcium levels caused by the "hungry bone" syndrome. Because of the severity of the bone disease, this fall can be much more marked and prolonged than after parathyroidectomy for primary hyperparathyroidism. Patients should receive daily oral calcitriol (0.5–1.0 μg) or some sort of intravenous active vitamin D sterol for 2–6 days before parathyroid surgery and during the postoperative period to stimulate intestinal calcium absorption and to maximize the effectiveness of oral calcium salts. Within 24–36 hours after surgery, marked hypocalcemia with serum calcium levels below 7–8 mg/dL may develop; thus, calcium gluconate should be initiated at a rate of 100 mg of calcium ion per hour in the operating room. Serum calcium should be measured every 4–6 hours and the calcium gluconate infusion rate increased if the serum calcium level continues to fall. The infusion rate may exceed 200 mg/h. Enteral calcium carbonate is initiated once the patient is able to tolerate oral intake, and doses as high as 1.0 g (elemental calcium) given four to six times daily, along with vitamin D sterol in excess of 1.0–2.0 μg/day (for calcitriol, doses of other agents vary according to their potency), are often needed for patients with marked hypocalcemia. Serum phosphorus levels may fall to subnormal levels postoperatively; phosphate treatment will markedly aggravate the hypocalcemia; however, patients should not be treated with phosphate unless serum phosphorus falls to below 2.0 mg/dL.[92]

Growth Hormone Therapy

rhGH should be considered in dialyzed children with growth failure that does not respond to optimization of nutrition, correction of acidosis, and control of ROD.[3,10] Serum phosphorus and PTH levels should be well controlled (both should be less than 1.5, the upper limit of the target range) prior to the initiation of rhGH in children with CKD.[93] rhGH therapy will increase serum PTH levels during the first months of therapy; therefore, serum PTH levels should be monitored monthly. rhGH therapy should be discontinued temporarily if PTH levels rise rapidly; however, it is important to note that GH also directly increases bone formation rate, independent of PTH values, thus distorting the relationship between PTH and bone formation rate.[70]

Children who are treated with maintenance dialysis respond less well to rhGH therapy than do children with less

severe CKD; the mechanisms for differences in response to GH therapy remain to be determined. Notably, bone formation rate increases out of proportion to changes in PTH values during treatment with rhGH, complicating the noninvasive assessment of ROD during therapy.[70] rhGH should be given at dosages of 0.045–0.05 mg/kg per day by daily subcutaneous injections until the patient has reached their final height or until renal transplantation.[3]

Summary

Understanding bone disease in kidney disease has increased over the years, but the clinical strategies currently employed to prevent the development of bone disease in children are still evolving. The management of bone disease in dialyzed children should include correction of hypocalcemia, maintenance of age-appropriate serum phosphorus, treatment of metabolic acidosis, maintenance of serum intact PTH levels within the currently recommended target ranges, and optimization of growth with rhGH.

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Management of Anemia in Children Undergoing Dialysis

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Introduction

Anemia is common and associated with adverse outcomes in children with chronic kidney disease. The management of anemia was dramatically changed due to the development of erythropoiesis-stimulating agents (ESAs) and new understandings of iron metabolism. As the adverse effects of anemia have become more apparent and concerning, there has been a push to optimize ESA and iron therapy. This chapter will review the basic management of anemia in children undergoing dialysis and should provide a practical approach to the day-to-day management of anemia in children who require renal replacement therapy.

The anemia of chronic kidney disease (CKD) is most often normocytic and normochromic. It is primarily due to the decreased production of endogenous erythropoietin (EPO) and, to a lesser degree, decreased responsiveness to the hormone, shortened red blood cell (RBC) survival, blood loss from frequent blood draws, and the hemodialysis (HD) procedure. Patients with CKD have a gradual decline in hemoglobin (Hb) over time as the level of glomerular filtration rate (GFR) declines. If left untreated, anemia of CKD has been associated not only with a multitude of adverse symptoms but also with higher morbidity, increased hospitalization days, and mortality in both adults and children.

Definition of Anemia

Anemia is defined as a decrease in RBC mass. In practice, anemia is determined by a low Hb and hematocrit (HCT) level relative to normative values based on gender and age. The World Health Organization has published Hb thresholds to classify individuals as anemic. Reference Hb concentration values have also been published using data from the U.S. National Health and Nutrition Examination Survey III (NHANES III), which included patients from age 1 year and over. The National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) definition of anemia has been taken from the NHANES III report. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines define anemia if the Hb concentration is < 11 g/dL in children 0.5–5 years, < 11.5 g/dL in children 5–12 years, and < 12 g/dL in children 12–15 years. Hb rather than HCT is considered a more accurate indicator of anemia since it is not affected by storage of the blood sample at room temperature, is more accurate in patients with hyperglycemia, is not affected by changes in plasma water, and is more reproducible when different automated counters are used.

Prevalence of Anemia in Chronic Kidney Disease

Anemia is associated with CKD of any cause, and the severity of the anemia is related to the degree of loss of GFR. This association has been reported in both adults and children. In a single-center, cross-sectional study of 366 children and adolescents with CKD, approximately 31% of patients with stage 1 and 29% of patients with stage 2 CKD reported prevalent anemia, defined as Hb < 12 mg/dL, whereas 66% of patients with stage 3 and 93% of patients with stages 4 and 5 CKD were anemic. Among children in the 2006 End Stage Renal Disease Clinical Performance Measures Project, 98% of 801 prevalent pediatric peritoneal dialysis (PD) patients were prescribed ESA.

In the Chronic Kidney Disease in Children Prospective Cohort Study (CkiD), the investigators found a linear decline in Hb below a threshold iohexol-determined GFR of 43 mL/min per 1.73 m^2, independent of age, race, gender, and underlying diagnosis. The Hb declined by 0.3 g/dL for every 5 mL/min per 1.73 m^2 decrease in GFR. Because serum creatinine-based estimated GFR may overestimate measured GFR in children, anemia might be seen even at early stages of CKD.

Other risk factors for the development of anemia include the use of angiotensin-converting enzyme (ACE) inhibitors, which may predispose to anemia by inhibiting erythropoiesis. An analysis by the International Pediatric Peritoneal

Dialysis Network found an association between low urine output, low serum albumin, high serum ferritin, and the use of bioincompatible dialysate with lower Hb levels.

The Effects of Anemia

The symptoms of anemia of CKD typically manifest gradually as the decline in Hb occurs slowly. Patients may report fatigue, weakness, decreased exercise tolerance, loss of appetite, dizziness, pallor, tachycardia, tachypnea, or chest pain.

Severe anemia in children with CKD has been associated with increases in cardiac workload and left ventricular hypertrophy (LVH). In a retrospective study that included pediatric dialysis patients, 75% of the children were noted to have LVH, but those with severe LVH had a significantly lower Hb level. Diastolic dysfunction has also been reported in children with CKD and has been associated with anemia. Treatment of anemia with ESA has been reported to have beneficial effects on cardiac parameters. In a blinded, crossover study of children undergoing PD and HD, patients were assigned to ESA or placebo. ESA produced a rise in mean Hb from 6.9 g/dL to 11.5 g/dL, which was associated with a significant fall in the cardiac index. Some patients had a reduction in the thickness of the interventricular septum and left ventricular posterior wall, but this did not reach statistical significance after 24 weeks. Cardiac performance also improves with the correction of anemia. In this study, children with end-stage renal disease (ESRD) performed treadmill tests before and 1 month and 6 months after ESA administration. There was a decrease in heart rate, decrease in resting oxygen consumption, and increase in exercise time.

Anemia of CKD is associated with higher morbidity, higher risk for hospitalization, and increased mortality. In an analysis of the North American Pediatric Renal Transplant Cooperative Studies (NAPRTCS) database, which included 1942 patients, a multivariate analysis demonstrated anemia (HCT <33%) to be associated with a 52% higher risk of death (adjusted relative risk (RR), 1.52; 95% confidence interval [CI], 1.03–2.26; $p = 0.037$). The presence of anemia was also associated with an increased risk for prolonged hospitalization, irrespective of dialysis modality (Warady and Ho, 2003), and was an independent risk factor for all-cause hospitalization in the pediatric predialysis CKD population.

Anemia also affects growth in children. An evaluation of the CKD registry of the NAPRTCS was used to evaluate factors associated with short stature in children with CKD. A total of 5615 patients were entered into the registry during the studied period, and investigators found that anemia (HCT below 33%) was an independent risk factor for short stature. In a retrospective study, catch-up growth was independently associated with Hb and ESA therapy. However, others have not found that correction of anemia with ESA improves the growth of children with CKD.

Anemia has been shown to cause changes in cognitive function, such as increases in reaction times and impairment in immediate and delayed memory. In another study, investigators evaluated the Wechsler intelligence score in 22 children with anemia of CKD treated with ESA. The investigators found that the Wechsler intelligence score increased in 11 children from 92 ± 16 to 97 ± 17 over the 12-month period ($p = 0.007$).

Anemia of CKD has a negative impact on several aspects of health-related quality of life. In a study of adolescent patients with CKD stages 1–5, including transplantation patients, anemic patients reported greater limitations in the quality-of-life questionnaire domains relating to (1) physical functioning, (2) limitations in schoolwork or activities with friends as a result of physical health, and (3) parental impact in time and family activities when compared to children without anemia. A more recent study compared child self-reported and parent proxy-reported health-related quality of life in children with CKD. Investigators found that patients with higher Hb had a better quality of life in the physical functioning category in parent proxy reports but not in child self-reports.

Testing for Anemia

The main cause of anemia in CKD is decreased production of EPO levels. Therefore, the initial laboratory evaluation is aimed at identifying other factors that may be contributing to the anemia. In particular, if the severity of anemia is disproportionate to the degree of renal dysfunction, there is evidence of iron deficiency, or there is evidence of leukopenia or thrombocytopenia. The NKF-KDOQI Guidelines recommend the following tests in the initial assessment of anemia: a complete blood count (CBC), absolute reticulocyte count, serum ferritin, and serum transferrin saturation (TSAT), or content of Hb in reticulocytes. The KDIGO guidelines suggest the same tests plus the addition of serum vitamin B_{12} and folate levels.

The CBC provides information about the severity of the anemia and adequacy of bone marrow function. Hb rather than HCT should be the standard measure for assessing anemia. For HD patients, the midweek predialysis sample is optimal. For PD patients, the timing of the sample is not critical as plasma volume does not fluctuate significantly. In addition to the Hb, the RBC indices provide valuable information. The anemia of CKD is in general normocytic and normochromic. Macrocytosis may indicate folate or vitamin B_{12} deficiency, whereas microcytosis may indicate iron deficiency or inherited disorders of Hb formation. Leukopenia and thrombocytopenia indicate a generalized disorder of the bone marrow, such as myelodysplasia. Abnormalities of the white blood cell count and differential or platelet count are not usual in anemia of CKD and may indicate other conditions.

The reticulocyte count is used to determine effective erythropoietic activity. Erythropoietin levels are not routinely measured.

Testing for Iron Deficiency

Although there are multiple laboratory tests aimed at determining the iron status of a patient, the KDIGO and the NKF-KDOQI anemia workgroups have recommended that ferritin and the TSAT be the primary indices used (see recommendations later). When compared to a functional gold standard of iron deficiency or an anatomical one (bone marrow stained for iron), most adult studies using a cutoff of 100 ng/mL have shown a sensitivity between 35% and 48%. In contrast, serum ferritin's specificity using the same cutoff is quite high (75%–100%), indicating that most CKD patients with levels below 100 ng/mL are truly iron deficient.

The diurnal and interlaboratory measurement variation of serum iron severely limits its value in determining iron deficiency. Instead, the circulating iron available for erythropoiesis is measured by the TSAT. It is calculated by dividing the total serum iron (the vast majority of which is bound to transferrin) by the total iron-binding capacity (TIBC), which reflects the total amount of transferrin in serum. Using a cutoff of 20%, TSAT's sensitivity ranges from 59% to 88%, while its specificity is slightly lower, 63%–78%.

Currently, the KDIGO 2012 practice guidelines for pediatric CKD 5D recommend intravenous (IV) iron administration during ESA therapy to maintain a serum ferritin greater than 100 ng/mL and a TSAT greater than 20%. These guidelines remain unchanged from the previous 2006 NKF-KDOQI guidelines for children. Given the lack of pediatric data, these recommendations are largely based on adult guidelines. One exception is the continued use of the lower 100 ng/mL ferritin cutoff for pediatric HD patients, while for adult HD patients, that cutoff had risen to 200 ng/mL in the 2006 NKF-KDOQI guidelines. In fact, in the KDIGO 2012 guidelines, the focus on adults has moved away from a lower limit with the recommendation that iron be given if the TSAT is $\leq$30% and the ferritin $\leq$500 ng/mL. Given the poor sensitivity of serum ferritin (especially at levels > 200 ng/mL) and the safety concerns of superphysiologic ferritin levels, the upper limit of ferritin remains undefined. While the KDIGO workgroup stated that "iron should not routinely be administered" above these levels, there is flexibility for a "therapeutic trial" of up to 1000 mg in patients with low Hb on high ESA doses.

In an attempt to address the limitations of serum ferritin and TSAT, several other markers of iron status have been proposed and examined. To date, reticulocyte Hb (CHr Hb) content appears to be the most promising, showing improved sensitivity and specificity over ferritin and TSAT in adult studies. CHr Hb is a measure of the amount of Hb in reticulocytes, and thus, given the very short life span of reticulocytes (1–2 days), it should reflect how much iron is available for incorporation into new RBCs. Additionally, CHr Hb is available on many of the current multichannel hematology analyzers that do CBCs. The current NKF-KDOQI guidelines include CHr Hb measures (cutoff 29 pg/cell) but have not been extended to pediatric CKD because the cutoff values remain unclear. A recent large retrospective study of approximately 600 pediatric ESRD patients from New Zealand examined the value of CHr Hb. Using a definition of an absolute iron deficiency of an Hb less than 10 mg/dL, a ferritin level less than 100 µg/L (100 ng/mL), and a TSAT less than 20%, a CHr Hb cut-off of 28.9 pg/cell gave a sensitivity of 90%, specificity of 75%, and an area under the curve (AUC) of 0.87. Interestingly, when the ferritin cut-off was left out of the model, the AUC dropped to 0.7.

Two other measures of iron status, which bear mentioning, include the percentage of hypochromic red cell (HRC) and soluble transferrin receptor (sTFR). HRC is a measure of the Hb concentration in RBCs by taking into account the absolute amount of Hgb as well as the size of the RBC. Its utility is likely compatible with CHr Hb. The UK's National Institute for Health and Care Excellence (NICE) guidelines using a 2016 meta-analysis now recommend an HRC of >6% as the most cost-effective means of diagnosing iron deficiency in adult HD patients. Unfortunately, the use of HRC in the United States has been hampered by the need for rapid analysis as red cells tend to expand while they are stored. sTFR levels reflect the expression of membrane transferrin receptors on premature erythroblasts and thus reflect the need for iron. In a situation where erythropoiesis has been stimulated by an ESA, and the patient does not have sufficient iron, sTFR levels rise. However, sTFR also provides an estimate of the erythroblast mass in the bone marrow. Thus, an ESA-treated patient may have a high sTFR due to iron deficiency or increased erythroblastic activity or a combination of both. Studies of sTFR in adult CKD have been mixed, and no clear cutoff has been established.

Vitamin and Mineral Deficiency

Vitamins and minerals play critical roles in erythropoiesis. The B vitamins are water-soluble and thus are removed during dialysis. Deficiency of vitamin B_{12} causes megaloblastic anemia because vitamin B_{12} is required for DNA synthesis. Individuals who are deficient have large erythrocytes due to the abnormal maturation process. Vitamin B_{12} is found only in products derived from animal sources; thus, vegetarians are at greater risk of becoming vitamin B_{12} deficient. Patients with gastrectomy, surgical removal of ileum, or chronic malabsorption disorder are more likely to have vitamin B_{12} deficiency. Vitamin B_{12} deficiency rarely occurs in patients receiving HD.

Folic acid deficiency also causes macrocytic anemia indistinguishable from vitamin B_{12} deficiency. Pyridoxine (vitamin B_6) deficiency causes microcytic anemia that can be easily confused with iron deficiency.

Vitamins developed for dialysis-dependent patients are excellent sources of water-soluble B vitamins. The addition of 0.25 mg/month of vitamin B_{12} may be necessary for selected patients. A weekly dose of 2–3 mg of folic acid and 100–150 mg of vitamin B_6 is recommended for adult HD patients receiving ESA therapy.

Vitamin C (1–1.5 g/week) was shown to overcome functional iron deficiency in patients with high ferritin levels. The recent development of vitamin E–coated HD membranes shows promise in improving ESA responsiveness in adult patients, although they have yet to be tested in pediatric patients.

Copper is an essential component of several enzymes that are required for blood formation. Factors that are associated with copper deficiency include prolonged diarrhea, premature birth, excessive zinc intake, and Menkes kinky hair syndrome that is due to a genetic defect in copper absorption. Copper deficiency causes an anemia that is very similar to iron deficiency. Cobalt, a critical component in the vitamin B_{12} molecule, is required in trace amounts for erythropoiesis. Cobalt deficiency is very rare.

Erythrocyte-Stimulating Agents

The ESAs include all agents that augment erythropoiesis through direct or indirect action on the EPO receptor, and they have become the hallmark of therapy for anemia of CKD. Overall, ESA therapy has been regarded as beneficial in attenuating the effects of anemia, as described earlier in this chapter. Furthermore, ESA treatment also reduces the need for blood transfusions and minimizes transfusion-associated risks (transmission of blood-borne viral infections, allosensitization, reactions, and transfusional hemosiderosis).

Presently, ESAs available include epoetin alpha and epoetin beta, which are considered short-acting, and darbepoetin and methoxy polyethylene glycol-epoetin beta, which are long-acting. Alternative ESAs continue to emerge, and epoetin biosimilar agents, which have minor differences in clinically inactive components to the reference biologic and have been used for over a decade in Europe, will likely play a larger role in the United States over time.

The choice of short-acting or long-acting ESA will depend on patient-specific issues, as it is widely accepted based on limited evidence that the ESA type does not affect patient outcomes. However, this notion was recently challenged by Sakaguchi and colleagues. Their analysis of a large registry-based cohort of nearly 200,000 HD patients in Japan revealed that the relative risk of death was 13% higher among long-acting ESA users compared with short-acting ESA users. Long-acting ESA use was associated with an increased rate of death from cardiovascular disease, infection, and malignancies. Similar observations in other geographic regions of the world have not been conducted, and ideally, prospective studies will be needed to confirm or invalidate these findings.

The initiation of ESA therapy in adults is considered when the Hb concentration falls below 10 g/dL. In children, there are limited data in order to recommend an Hb threshold. The KDIGO guidelines recommend basing the initiation of ESA after considering all potential benefits and potential harms. The goal of ESA therapy is to increase the Hb at a rate of 1 to 2 g/dL per month with a target Hb of 11–12 g/dL. The Hb should not exceed 13 g/dL in ESA-treated patients. The NKF-KDOQI guidelines recommend that children on dialysis who initiate ESA therapy have their Hb monitored every 2 weeks. Once the target Hb level has been reached and the patient is on a stable ESA dose, monitoring every 4 weeks is recommended. Hb levels should be followed more closely after making a significant change to the ESA dose. Dose adjustments are indicated if the Hb is rapidly approaching or is above the target level, if the Hb increases by more than 1.3 g/dL in a 2-week period, or if the Hb fails to increase 1.6–2 g/dL over a period of 8 weeks.

ESA can be given intravenously or subcutaneously. The route of administration of ESA will be determined by patient-oriented issues, treatment setting, efficacy considerations, and the class of ESA being prescribed. For patients undergoing PD, subcutaneous administration is the only route feasible. For those patients undergoing HD, IV, or subcutaneous administration is possible. In children, subcutaneous injections are uncomfortable, and the IV route is generally recommended for those patients on HD.

The dose of ESA in children will vary depending on the age of the child, the route of administration, and the mode of dialysis. Epoetin alpha and epoetin beta dosing usually start at 50 IU/kg body weight three times per week. However, young children will require higher EPO doses. Data from NAPRTCS reported that children younger than 1 year of age received an average of 350 IU/kg/week, those 2–5 years of age received 275 IU/kg/week, those 6–12 years of age needed 250 IU/kg/week, while those older than 12 years needed 200 IU/kg/week. Treatment with epoetin biosimilar agents should mirror that with the originator epoetin. Patients should be started at the same dose, and dose titration should be similar. A reduction in dosing is possible when EPO is given subcutaneously rather than intravenously. Children on HD require higher EPO doses per week when compared to children on PD. It has been proposed that this is due to greater blood loss during HD treatment.

Darbepoetin alpha is a hyperglycosylated form of EPO. It differs as it contains five N-linked oligosaccharide chains instead of three chains. Pharmacokinetic studies in children show that the half-life of darbepoetin in children is similar to adults. Following IV administration to patients receiving dialysis, the terminal half-life was reported to be 22 hours and approximately threefold longer than that of epoetin alpha. Following subcutaneous administration, the average terminal half-life was 42 hours. Usually, dosing starts at 0.45 µg/kg body weight (dosing range, 0.25–0.75 µg/kg body weight) once every 1–2 weeks. Investigators have proposed a conversion dose of erythopoietin alpha to dabepoietin to be 0.5 µg for every 200 IU of erythropoietin alpha rather than the 1 µg/200 IU conversion recommended by the manufacturer. In an open-label study involving patients aged 1–18 years of age,

dabepoietin was reported to be noninferior to EPO in the treatment of anemia of CKD.

Methoxy polyethylene glycol-epoetin beta is an erythropoietin continuous receptor activator with an increased half-life when compared to erythropoietin. Following an IV administration of 0.4 μg/kg body weight to CKD patients receiving PD, the terminal half-life was 134 ± 65 hours (mean ± SD). After a subcutaneous administration of 0.8 μg/kg to CKD patients receiving PD, the terminal half-life was 139 ± 67 hours. The initial dose is 0.6 μg/kg of body weight every 2 weeks administered subcutaneously or intravenously. Its safety and efficacy have not been rigorously evaluated in children. In one study, 16 children on PD were converted to subcutaneous methoxy polyethylene glycol-epoetin beta scheduled every 2 weeks. The follow-up period was 6 months. The medication dose was increased from 0.86 ± 0.33 to 1.67 ± 0.4 μg/kg at month 3 and was 1.6 ± 0.67 μg/kg at the end of the study. The Hb levels were maintained, and no adverse events were observed during the protocol.

Lack of Response to Erythropoiesis-Stimulating Agent

Erythropoietin resistance or failure to respond to ESA is recognized with the inability to maintain a constant Hb level with increasing doses of ESA (typically in excess of 500 IU/kg/week) or if there is a decrease in Hb levels with the use of a constant ESA dose. The etiology of ESA resistance includes infection/inflammation (probably mediated in part by high hepcidin levels), absolute iron deficiency, secondary hyperparathyroidism, chronic blood loss, vitamin B_{12}/folate deficiency, use of ACE inhibitors or angiotensin-receptor blockers, malnutrition, underdialysis, hemoglobinopathies, and rarely antibody-mediated pure red cell aplasia. Some of the conditions that cause hyporesponsiveness are reversible and addressing the implicating factors will result in improved response to ESA. Furthermore, not all causes of failure to respond to ESA are readily apparent, and some patients require evaluation for the more unusual causes listed earlier.

Risk of Adverse Outcomes

Hypertension is the most common adverse effect attributed to ESA therapy. Patients can experience de novo hypertension or worsening of chronic hypertension. In children, an increase in antihypertensive therapy occurred in 30% of those treated with ESA. Several mechanisms have been considered in the pathogenesis of ESA-induced hypertension. These include the possible role of the rise of HCT and erythrocyte mass, changes in production or sensitivity to endogenous vasopressors, alterations in vascular smooth-muscle ionic milieu, dysregulation of production or responsiveness to endogenous vasodilatory factors, a direct vasopressor action of EPO, and finally arterial remodeling through stimulation of vascular cell growth. If the hypertension is significant, temporary discontinuation or reduction in the dose of ESA as well as administration of antihypertensive treatment may be indicated.

There are no controlled clinical trials in children that have evaluated other outcomes, such as risk of death, stroke, congestive heart failure, thrombosis of HD vascular access, and other thromboembolic events with regard to ESA use or higher Hb targets as in the adult population.

Iron Therapy

Oral Iron Supplementation

Iron supplements are necessary to meet the demand for increased erythropoiesis during ESA therapy in children with CKD. The current KDIGO guidelines and NICE guidelines again closely follow adult recommendations and state that oral therapy is likely adequate for nondialysis and PD patients, while HD patients likely require IV iron therapy (see later). However, some investigators have advocated for oral iron therapy in pediatric HD patients. One small, randomized trial of 35 pediatric HD patients demonstrated that while IV iron did result in increased ferritin levels, it did not show a significant advantage over oral iron in terms of maintaining adequate iron stores for erythropoiesis. It is important to note that at the beginning of this trial, all patients were iron replete by current KDIGO standards. Additionally, most adult studies of HD patients have shown that IV iron is superior to oral iron.

Oral iron is usually dosed at 3–6 mg/kg/day of elemental iron given twice daily with a maximum dose of 300 mg/day. Generally, the dose should be taken at least 2 hours before or 1 hour after phosphate binders and food to maximize absorption. Coadministration of iron with other medications, such as phosphate binders and antacids, limit its absorption due to changes in gastric pH. As an aside, oral iron preparations can be used as phosphorus binders but have not been widely marketed as such. High-dose vitamin C has been found to enhance iron absorption in the gut but has the potential side effect of oxalate deposition in the presence of decreased kidney function. Compliance with oral iron therapy in children can be limited by gastrointestinal intolerance, which is dose related and occur in up to 20% of patients. Additionally, the use of oral suspension can cause teeth discoloration and staining.

There is a multitude of oral iron preparations available with varying amounts of elemental iron, including ferrous sulfate, ferrous fumarate, ferrous gluconate, ferrous succinate, iron polymaltose, and polysaccharide–iron complex. Ferrous sulfate is the most commonly prescribed iron compound containing 65 mg of elemental iron per 325 mg tablet. There is very limited data comparing the efficacy of one preparation versus another in CKD

patients. One small study of 46 adults on HD randomized patients to receive 200 mg of elemental iron daily in one of four preparations (1) Chromagen (ferrous fumarate), (2) Feosol (ferrous sulfate), (3) Niferex (polysaccharide iron complex), or (4) Tabron (ferrous fumarate). Although the Tabron group tended to have the highest percentage of patients with a TSAT > 20%, followed by the Feosol, Chromagen, and Niferex groups, these differences were not statistically significant. Importantly, despite intensive compliance monitoring during the study, the mean HCT remained below 30%, and the mean TSAT remained below 20% in three of the four groups, reinforcing the poor efficacy of oral iron supplementation in HD patients.

Recently, there has been growing interest in the use of oral ferric citrate as both a phosphate binder and an iron supplement. Studies indicate that in adults, ferric citrate is safe and effective as a phosphorus binder with common adverse effects of diarrhea, nausea, vomiting, and constipation. Its use also appears to increase iron stores and reduce the need for IV iron and ESA use while maintaining Hb levels in adult HD patients. There are little data describing its use in children. A retrospective cohort of 11 pediatric dialysis patients (5 HD and 6 PD) noted a decrease in serum phosphate, improved iron status, and stable Hb using oral ferric citrate. Average age-adjusted phosphorus levels decreased from the 99th to the 81st percentile. Therapy was well tolerated, and although there were some adverse gastrointestinal effects, no patients discontinued therapy. Given its ability to induce a decrease in fibroblast growth factor 23 (FGF-23) levels in adults, ferric citrate may be a promising combination phosphate binder and iron supplement.

Intravenous Iron Supplementation

As stated previously, the current KDIGO and NICE guidelines recommend IV iron as the preferred route of administration in HD patients. These recommendations are based on both adult and pediatric data. Specifically, evidence in adult patients comes from several randomized control trials comparing IV to oral iron that demonstrated that IV iron administration is superior to oral iron in HD patients. In pediatric patients, there are several prospective randomized trials showing that IV iron is effective in repleting and maintaining iron stores in children on HD. In the case of pediatric PD patients, IV iron is often only administered after the patient has not shown a response to a course of oral iron. This is likely a function of the overall decreased need for iron in PD patients due to their much smaller obligate blood loss, the lack of easy IV access, and the inconvenience of the small but frequent dosing strategies used in HD patients.

In general, treatment with IV iron is broken down in a loading phase where consecutive doses are given in order to replete the patient's iron stores and then a maintenance phase where a smaller dose is given once a week. Currently, four iron preparations are available for parenteral use in dialysis patients within the United States (refer to the following IV iron table), with a fifth (ferric carboxymaltose) approved for use in nondialysis patients. Additionally, iron isomaltoside is available in Europe. These different preparations avoid the toxicity of an iron salt by complexing it with a carbohydrate (i.e., dextran, sucrose, or gluconate). Before the iron within these parenteral compounds can be used directly for erythropoiesis, it must first be processed by the reticuloendothelial system.

IV iron table

Intravenous Iron Preparation	Dose	Frequency	
		Loading	Maintenance
Iron dextran INFeD: 50 mg/mL (2 mL vials) DexFerrum: 50 mg/mL (2 mL vials) **(no longer available in the United States)**	4 mg/kg/dose not to exceed 100 mg Test dose: Child < 10 kg: 10 mg Child 10–25 kg: 15 mg Child > 25 kg: 25 mg	Three times weekly for a total of 8–10 dialysis sessions	Once a week
Sodium ferric gluconate Ferrlecit: 12.5 mg/mL (5 mL vials)	1.5–3 mg/kg/dose not to exceed 125 mg	Three times weekly for a total of eight dialysis sessions	Once a week
Iron sucrose Venofer: 20 mg/mL (5 mL vials)	1–4 mg/kg/dose not to exceed 100 mg	Three times weekly for a total of 10 dialysis sessions	Once a week
Ferric pyrophosphate citrate	Please see text	N/A	Every session

Iron dextran, a complex of ferric oxyhydroxide with polymerized dextran, was the first parenteral formulation to become available for the treatment of iron deficiency. Until recently, it was the only parenteral compound that had the advantage of a single infusion up to 1 g, which is both convenient and cost effective. However, its popularity has decreased due to the Food and Drug Administration (FDA) black-box warning of potentially fatal anaphylaxis, which has been estimated at 0.6%–0.7%. Hence, a test dose of 10–25 mg is required before the full infusion to check for the possibility of an allergic response. Other reported adverse reactions that are not thought to be immune mediated include delayed reactions of hypotension, arthralgias, myalgias, malaise, abdominal pain, nausea, and vomiting. Of the two forms, INFeD and DexFerrum, only the former is currently available within the United States, likely due to a lower incidence of adverse effects.

Sodium ferric gluconate, a complex of sodium ferric gluconate in sucrose that was FDA approved in 1999, has a lower rate of adverse reactions with no fatal hypersensitivity reactions reported to date. Ferric gluconate has had an allergy-event reporting rate of 3.3 episodes per million doses compared to 8.7 with iron dextran, and although when it was first marketed, a test dose was recommended, that recommendation has been dropped. An international prospective multicenter trial of 66 pediatric patients investigated the safety and efficacy of ferric gluconate at both a 1.5 mg/kg dose and a 3 mg/kg dose over eight consecutive doses in pediatric HD patients on ESA therapy. Both dosing regimens resulted in significant increases in mean Hb, HCT, TSAT, serum ferritin, and reticulocyte Hb content, with no unexpected adverse reaction reported. Another multicenter study of 23 pediatric HD patients showed that a weekly ferric gluconate dose of 1 mg/kg was effective as a maintenance regimen.

Iron sucrose, a complex of iron hydroxide and sucrose, was FDA approved in 2000. Several studies have demonstrated its effectiveness, and like ferric gluconate, it is well tolerated, with minimal adverse effects. Dosing in children is 1–4 mg/kg weekly for 12 weeks. In a study by Morgan et al., iron sucrose was successfully used in pediatric HD patients at a dose of 2 mg/kg/week. No adverse events were reported even when patients with suspected iron deficiency received a single loading dose of 7 mg/kg (maximum of 200 mg), followed by 2 mg/kg/week. Another study of 14 pediatric HD patients concluded that dosages of 1 mg/kg/dialysis and 0.3 mg/kg/dialysis were sufficient for loading and maintenance therapy, respectively.

Ferumoxytol was approved by the FDA in 2009. It is a novel iron oxide nanoparticle with a polyglucose sorbitol carboxymethyl ether coating. Although it was initially approved as safe and effective in adult CKD patients when administered as a single rapid dose of up to 510 mg, there have been 79 reports of anaphylactic reactions resulting in 18 deaths. Thus, in 2015, the FDA issued a black-box warning, including that ferumoxytol must be given as a diluted IV infusion over a minimum of 15 minutes. Data describing its dosing and use in pediatric patients are lacking.

Finally, ferric carboxymaltose, a polynuclear iron (III)–hydroxide carbohydrate complex, was approved by the FDA in 2013 for use in nondialysis adult CKD patients. Although there are no data describing its use in children, there have been studies indicating its efficacy in adult dialysis patients.

Intradialytic Iron Supplementation

Ferric pyrophosphate citrate (FPC) is a low-molecular-weight iron salt that can be administered via the dialysate, where it crosses the hemodialyzer membrane and enters the blood. Because it donates iron directly to transferrin, unlike the previous iron compounds, it does not require processing by macrophages and, in theory, could bypass the reticuloendothelial blockade. Adult studies have indicated that it could effectively deliver sufficient iron to replace ongoing losses and maintain Hb, leading to its approval by the FDA in 2015. Treatment with FPC did not increase ferritin, possibly reflecting that it does not increase iron stores and thus carries less risk of iron overload. It is currently being investigated as a new means of meeting the increased maintenance iron requirements of pediatric patients receiving HD. A recent pharmacokinetic and safety study of FPC via dialysate and IV in 22 HD patients ages 1–18 supports the use of FPC as a maintenance form of iron in this population. Essentially delivering FPC via dialysate or IV was very well tolerated and delivered 0.06 to 0.1 mg of iron per kilogram over a standard HD session. Clearly, future larger studies are needed, but this may become a safe and efficient way of delivering iron in pediatric dialysis patients.

Iron Safety

While the use of ESAs, often at high doses, has been embraced by nephrologists, iron therapy has been approached rather conservatively. Ironically, there are now important safety concerns with the use of ESAs while the data linking iron administration to poorer outcomes remain lacking. Much of the discomfort with iron administration can be attributed to problems of iron overload as a result of multiple transfusions during the pre-ESA era. In addition, several observational studies have described an association between high serum ferritin levels and infection or mortality. However, the acute phase reactant behavior of ferritin remains a large confounding factor as increased ferritin levels do not necessarily reflect the iron status and instead may simply be due to increased levels of inflammation present in CKD patients. Thus, the link between high ferritin levels and infection and mortality may be an epiphenomenon. Indeed, while no randomized controlled study of whether intravenous iron therapy leads to an increased risk of infection or

death has been performed, a retrospective epidemiological study of 50,000 + HD patients found that iron administration was associated with improved survival. The PIVOTAL trial, which enrolled 2141 HD adult patients from 50 centers undergoing HD, has recently provided further evidence of the safety of IV iron supplementation in patients with a ferritin level as high as 700 ng/mL. Patients were randomized to either a proactive high-dose or a reactive low-dose iron regimen. Interestingly, there was a lower rate of primary cardiovascular events in the high-dose cohort and no difference in infection rates versus the low-dose cohort. Additionally, the high-dose group had less ESA administration. Finally, many of the concerns regarding the adverse effects of iron, including oxidative stress, are based on in vitro studies. Regardless, when one considers the benefits of improved response to ESA agents, the overall risk-benefit ratio favors the use of IV iron in HD patients.

As far as the upper limit of ferritin, most investigators agree that extremely high levels (> 2000 ng/mL) are reflective of simple iron overload or hemosiderosis. Levels of greater than 1200 ng/mL are still associated with increased mortality risk even after adjustment for markers of malnutrition and inflammation. Thus most clinicians would feel uncomfortable with the use of IV iron at these high ferritin levels. In contrast, it remains unclear if therapy with IV iron is warranted at ferritin levels between 500 and 1200 ng/mL, even when the TSAT is less than 20%. The results of the DRIVE study did demonstrate that IV iron therapy in patients with a serum ferritin between 500 and 1200 ng/mL resulted in a 25% reduction in ESA dose. Additionally, the large retrospective study of 50,000 + dialysis patients mentioned earlier showed that the greatest ESA responsiveness occurred in patients with a TSAT of 30%–50% and a ferritin level of 800–1200 ng/mL. However, the lack of randomized controlled trials comparing the safety and efficacy of targeting ferritin levels greater than 500 ng/mL versus less than 500 ng/mL has led to the KDIGO guidelines reemphasizing the old NKF-KDOQI guidelines that "when ferritin level is greater than 500 ng/mL, decisions regarding IV iron administration should weigh ESA responsiveness, Hgb and TSAT level, and the patient's clinical status."

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Prevention and Treatment of Cardiovascular Complications in Children Undergoing Dialysis

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Cardiovascular Mortality in Children on Maintenance Dialysis

Reports from international registries since 2000 have confirmed, that like in adults, cardiovascular disease (CVD) is the leading cause of death in children with end-stage renal disease (ESRD) and young adults with childhood onset of CKD. There has been some improvement in mortality rates; however, it still remains about 30 times higher than in the general pediatric population. Not surprisingly, recently updated American Heart Association guidelines for cardiovascular (CV) risk reduction in high-risk pediatric patients continue to stratify pediatric patients with ESRD in the "highest risk" category for the development of CVD.

Of the specific causes of CV deaths, cardiac arrest is the most common. These causes are different from those of adults. In adults, coronary artery disease and congestive heart failure due to cardiomyopathy are two leading causes of mortality from CVD. The mortality from these causes is extremely low in children and adults younger than 30 years of age. The high rate of sudden death in children, especially in infants with ESRD, is poorly understood and warrants further investigation. The risk factors and pathogenic mechanisms leading to CVD in adults who had the onset of chronic kidney disease (CKD) in childhood are better understood than are those producing cardiac morbidity and mortality in children. The recent study by Modi et al. confirmed that diabetes, coronary artery disease, and heart failure were notable risk factors for CV-related mortality in young adults with childhood onset of ESRD. This chapter will focus on the prevention of the "classic" form of CVD as seen in adults who developed CKD in childhood.

Development of Cardiovascular Disease in Children with Chronic Kidney Disease

There are two groups of risk factors responsible for accelerated CVD in adults with ESRD. First, compared to the nonuremic population, there is an overrepresentation of classical risk factors, e.g., diabetes, hypertension, and hyperlipidemia. A majority of the adults who develop ESRD do so as a complication of diabetes or generalized atherosclerosis. Often, cardiac disease antedates the onset of CKD in these patients. Second, there are numerous uremia-related risk factors, such as dyslipidemia, anemia, inflammation, infection, abnormal calcium-phosphorus metabolism, and oxidative stress, that may singly or in concert, trigger the development of CVD. Many of the same risk factors are present in high frequency in children on dialysis, making them extremely susceptible to CVD.

There are two parallel processes involved in the development of CVD in children with ESRD. The first is uremic cardiomyopathy. It is initially manifest by disorders of the left ventricle (LV), which lead to adoptive LV remodeling. Two types of LV remodeling are recognized. Concentric LV hypertrophy (LVH) results primarily from pressure overload, as occurs with hypertension. Eccentric LVH has been related primarily to volume overload as frequently seen in patients on dialysis or with severe anemia. It is likely that the effects of hemodynamic overload on the LV are augmented by other nonhemodynamic causes such as high levels of fibroblast growth factor 23 (FGF23), sympathetic hyperactivity, systemic inflammation, and local production of angiotensin II. With time, a maladaptive phase of LVH develops, characterized by decreased capillary density, decreased coronary reserve and subendocardial perfusion, a tendency to arrhythmia, and the development of myocardial fibrosis. All this

leads to myocyte death and, finally, to diastolic and systolic dysfunction. Symptomatic cardiomyopathy is very rare in children, but early abnormalities of cardiac structure and function can be seen frequently. LVH develops when CKD is mild or moderate in children and progresses as renal function deteriorates. LVH is very common (52%–75%) during long-term dialysis. Both concentric and eccentric geometric patterns of LVH are present in these patients, suggesting that, as in adults with ESRD, the mechanism of LVH in advanced CKD in children is volume and pressure overload. LVH is prevalent in both children on hemodialysis and peritoneal dialysis. Small retrospective studies suggest that with good blood pressure (BP) and anemia control, LVH will regress in young patients on dialysis. In contrast to adults, with whom systolic dysfunction is frequently associated with early cardiac failure and decreased survival, in children, systolic LV function is usually preserved. On the other hand, these children may develop LV diastolic dysfunction, often the initial manifestation of abnormal cardiac function. Small studies also indicate that, like in adults, myocardial stunning can be present in children indicating decreased perfusion during a dialysis session.

The second process involves accelerated vascular injury, which manifests by arterial hypertrophy and stiffness. This leads to arterio- and atherosclerosis. Children on dialysis have a high prevalence of asymptomatic vascular disease, as demonstrated by abnormal carotid intima-medial thickness (IMT), diminished arterial wall compliance, and coronary artery calcification. This eventually leads to symptomatic (ischemic) coronary artery disease in young adults with childhood onset of ESRD. In ESRD patients, a variety of factors have been associated with the development of atherosclerosis. Many of these factors are similar to those involved in the development of cardiac hypertrophy and include hypertension, dyslipidemia, abnormal calcium-phosphorus metabolism, chronic inflammation, and others.

Evaluation and Treatment Recommendations

The overall strategy in prevention of CV complications in children with ESRD is avoidance of long-term dialysis. The goal is to prevent development and delay the progression of cardiomyopathy and atherosclerosis. Even though kidney transplantation poses continuous CV risk (hypertension, hyperlipidemia, allograft dysfunction), it eliminates many uremia-related risks, reduces risk of cardiac death by approximately 80%, and prolongs life span by 20–30 years. A recent study showed that graft failure after the first kidney transplant was associated with almost five times higher mortality rate as compared to children with a functioning graft. Having maintenance dialysis even for a few months before a transplant was also associated with worse survival in this study. Thus, preemptive kidney transplantation should be the ultimate goal to minimize CV morbidity and mortality. Recent pediatric studies, like in adults, indicate that initiation of dialysis at a relatively high (> 10–12 mL/min/1.73 m^2) estimated glomerular filtration rate (eGFR) was associated with worse survival when compared to initiation at lower eGFR. Delayed initiation of dialysis, if this can be safely achieved, may be beneficial by postponing exposure to the psychological and physical burdens that are associated with chronic dialysis therapy, and especially important in this regard is the progression of CVD in children on dialysis. While CV risk factors and subclinical cardiac and vascular abnormalities are present in children prior to dialysis, CVD quickly accelerates after dialysis initiation. Thus, delaying initiation of dialysis for a few months might prevent the development or progression of CVD. For those patients who must have long-term dialysis, the strategy is directly linked to the achievement of adequate dialysis outcomes, which include aggressive monitoring and management of hypertension, dyslipidemia, calcium-phosphorus metabolism, anemia, nutrition, systemic inflammation, and other dialysis complications.

Echocardiographic Evaluation

The Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients recommend that children have an echocardiographic evaluation for the presence of cardiac disease (cardiomyopathy and valvular disease) at the time of initiation of dialysis therapy. As discussed earlier, the most common cardiac diagnosis in children on chronic dialysis is hypertrophic cardiomyopathy or LVH. There is no uniform definition of LVH in children, which makes it difficult to establish specific targets for left ventricular mass (LVM). The most commonly used definition of LVH is based on the 95th percentile of LVM indexed to height raised to the power of 2.7 ($g/m^{2.7}$). For children older than 8 years of age, left ventricular mass index (LVMI) > 51 $g/m^{2.7}$ can be used as a clinically significant marker of LVH. If LVH is diagnosed at the time of initiation of dialysis, routine echocardiographic monitoring every 6 months is advisable. If the initial echocardiogram is normal, yearly echocardiographic follow-up is suggested. Echocardiography is also important to monitor cardiac function. Shortening fraction, index of systolic function, is routinely calculated from echocardiographic parameters. Systolic dysfunction is rare in children on dialysis, but if discovered, the patient should be evaluated by a cardiologist.

Hypertension

The target BP in children with CKD, including those on dialysis, should be less than the 90th percentile adjusted for age, gender, and height of less than 120/80 mm Hg for children 13 years of age and older. About three-quarters of children entering maintenance dialysis therapy have BP in the hypertensive range despite many of them receiving antihypertensive medications, and hypertension is unlikely to improve during long-term dialysis. Hypertension is frequent with both hemodialysis and peritoneal dialysis but

is reported to be more frequent in hemodialyzed children. Poor BP control in children on maintenance dialysis is multifactorial, but the major cause is fluid overload. Thus, the first step in the diagnosis and management of hypertension in children on dialysis should be an evaluation of volume status. Unfortunately, many children on dialysis do not achieve their dry weight. Volume status assessment in young patients is frequently not accurate. This is one of the reasons that the frequency of hypertension is higher in young children. In addition, correct assessment of BP is difficult in small children, and consequently, it is frequently underdiagnosed and therefore not adequately treated. Another group of children who presents with significant fluid overload and, therefore, with hypertension is adolescents, who are almost always noncompliant with fluid and salt restriction. Chronic fluid overload resulting in hypertension is the major cause of LVH in children on chronic dialysis. Thus, aggressive management of fluid overload and achievement of dry weight is the most effective treatment of hypertension and LVH in children on chronic dialysis. For children on hemodialysis, longer and more frequent dialysis sessions and, sometimes, even intermittent ultrafiltration might be needed to improve volume status.

In most children, the achievement of dry weight results in normalization of BP and a significant decrease in the use of antihypertensive medications. If BP remains elevated despite adequate volume control, antihypertensive medications should be optimized. Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers should be considered the first line of therapy in children on dialysis because of their renal and cardioprotective effects. Addition of calcium channel blockers or beta-blockers should be tried next. It is important to remember that if effective dry weight is not achieved, antihypertensive meds, especially vasodilators and beta-blockers, will likely not work and may further impair the ability to remove fluid. If BP is still inadequately controlled after achieving dry weight and maximizing the use of BP medications, nephrectomies should be strongly considered.

Achievement of normal daytime office BP measurement does not necessarily contemplate the absence of hypertension. Patients with CKD frequently have undetected nighttime hypertension. Children who have normal BP taking in the dialysis unit might benefit from ambulatory BP monitoring to investigate the presence of nighttime hypertension.

Dyslipidemia

Dyslipidemia is very prevalent in children on chronic dialysis and is characterized by low high-density lipoprotein (HDL) and high triglyceride levels. Many children also have increased total cholesterol and low-density lipoprotein (LDL) levels. Kidney Disease: Improving Global Outcomes (KDIGO) recommends evaluation of dyslipidemias in adolescents upon presentation with CKD stage 5 (glomerular filtration rate [GFR] < 15 mL/min/1.73 m^2 or on dialysis), at 2–3 months after a change in treatment or other conditions known to cause dyslipidemias, and at least annually thereafter. Reasons to repeat lipid measurements after 2–3 months include changes in kidney replacement therapy modality, treatment with diet or lipid-lowering agents, immunosuppressive agents that affect lipids (e.g., prednisone, cyclosporine, or sirolimus), or other changes that may affect plasma lipids. The assessment of dyslipidemias should include a complete fasting lipid profile with total cholesterol, LDL, HDL, and triglycerides. The definition of dyslipidemia differs in children and adults. Hyperlipidemia in children is defined as lipid levels greater than the 95th percentile for age and gender. The normative data for lipids in children and adolescents currently used are from Lipid Research Clinics Program from the National Institutes of Health (NIH) published in 1980 and can be found in the most recent KDIGO guidelines for the management of dyslipidemias in CKD.

For adolescents with stage 5 CKD and a level of LDL ≥ 130 mg/dL, KDOQI recommends treatment to reduce LDL to < 130 mg/dL. If LDL is < 130 mg/dL, fasting triglycerides is ≥ 200 mg/dL, and non-HDL cholesterol (total cholesterol minus HDL) is ≥ 160 mg/dL, treatment should be considered to reduce non-HDL cholesterol to < 160 mg/dL. Due to limited statin use in children with CKD and dialysis, KDIGO guidelines do not recommend the use of statins in children aged < 10 years. However, the Working Group emphasized that patients (boys aged > 10 years and postmenarchal girls) with severely elevated LDL-C (> 190 mg/dL) or with multiple additional CV risk factors, such as a family history of premature coronary disease, diabetes, hypertension, smoking, and ESRD, might be candidates for statin use (lowest dose possible). All children with dyslipidemias should follow the recommendations for therapeutic lifestyle changes (TLCs), which include diet modification with reduction in saturated fat intake, increase in fiber intake, and moderate physical activity. Adolescents should be counseled about avoiding smoking. Unfortunately, noncompliance with TLCs is one of the major problems in the management of dyslipidemia in adolescents. Pediatric nephrologists must also recognize that appropriate caloric intake, including calories from fat, should be emphasized to avoid malnutrition and ensure normal growth and development, especially in young children.

Abnormal Calcium–Phosphorus Metabolism

The Working Group on Cardiovascular Disease in Dialysis Patients recommends maintaining calcium (Ca) and phosphorus (P) levels within the normal range and the Ca × P product < 55 mg^2/dL^2 in children on chronic dialysis. These recommendations are based on adult studies demonstrating that hyperphosphatemia and increased Ca × P product are strongly correlated with cardiac calcification and increased cardiac morbidity and mortality. Majority of children on chronic dialysis are hyperphosphatemic and, as a result, require phosphate-binding therapy. Studies of children and young adults on chronic dialysis determined that the

cumulative dose of calcium-based phosphate binders and the administration of active vitamin D preparations are strong determinants of arterial stiffness, coronary artery calcification, and metastatic calcinosis. This may represent risk factors for CVD that are, perhaps, even more important than hypertension and dyslipidemia. Therefore, the use of non-calcium-based phosphate binders, careful monitoring of serum calcium level, and appropriate adjustment of the dose of vitamin D to avoid hypercalcemia are essential in the management of children on dialysis to prevent the development and progression of CV abnormalities.

Anemia

Studies in adult dialysis patients have identified anemia as a risk factor for patient morbidity and mortality. The studies from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) indicate that anemia is very common and is frequently undertreated in children on chronic dialysis. The NAPRTCS data also showed that anemia is present in more than half the children entering maintenance dialysis and is associated with a 52% higher risk of death in chronically dialyzed children. A few small single-center pediatric studies determined that anemic children more frequently have LVH than those with normal hemoglobin and that treatment of severe anemia with erythropoietin results in a significant reduction of LVM index. Recent analysis from the Pediatric Peritoneal Dialysis Network (IPPN) indicated that anemia remains a significant problem despite the almost universal use of erythropoiesis-stimulating agents (ESAs). In their analysis, ESA resistance was associated with inflammation, fluid retention, and hyperparathyroidism. Importantly, anemia and high ESA dose requirements (reflecting treatment resistance) independently predicted mortality.

The hemoglobin level of 11.0 g/dL represents the value < 5th percentile for boys younger than 5 years, 11.5 g/dL for boys 6–8 years, 12.0–12.5 g/dL for boys 9–14 years, and 13.5 for boys 15–19 years. For girls of all ages, the lower limits of normal values are 11–12 g/dL. Current KDOQI guidelines for treatment of anemia recommend keeping the hemoglobin level above 11 g/dL by using an appropriate iron therapy and recombinant erythropoietin. In the opinion of the Working Group, there is insufficient evidence to recommend routinely maintaining hemoglobin levels above 13 g/dL or greater. These target levels are about 2 g/dL less than the mean hemoglobin values for children in each age category. They are based on adult data showing that higher hemoglobin levels in hemodialyzed patients with heart disease were associated with an increased rate of nonfatal myocardial infarction. Since symptomatic CVD, including myocardial infarction, is extremely rare in children, the results from these adult studies and, therefore, current hemoglobin targets might not be applicable to pediatric patients. Unfortunately, for recombinant erythropoietin therapy reimbursement in children with CKD, Medicare and insurance companies follow current KDIGO guidelines to keep an upper limit of hematocrit levels at 36%. These guidelines apply even to children who are not yet on dialysis, possibly putting them at risk for CVD prior to initiation of chronic dialysis therapy.

Malnutrition and Inflammation

Adequate nutrition is an essential part of dialysis care. Malnutrition is frequent in children on chronic dialysis, especially in young patients and those who require long-term dialysis. Failure to thrive and hypoalbuminemia are significant risks of death in pediatric patients with ESRD. Studies in adults on chronic dialysis have shown low BP, low body mass index (BMI), and low serum cholesterol are often correlated with an unfavorable clinical outcome. Thus, whereas traditional risk factors of CVD are correlated with an unfavorable outcome in the general population and patients with CKD not yet on dialysis, in dialyzed patients, mild hypertension, hypercholesterolemia, and overweight appear to be protective and associated with an improved survival. It has been speculated that malnutrition–inflammation–atherosclerosis complex underlies, at least partly, the phenomenon of "reverse epidemiology," since malnutrition causes a low BMI and hypocholesterolemia. More current studies focus on protein-energy wasting (PEW), a condition frequently found in dialyzed patients. As in adults, a small proportion of children with CKD also develop PEW. In a recent study, children who lost weight while on maintenance dialysis had worse survival than children with stable weight. This suggests that emphasis should be placed on the assessment and management of nontraditional CV risks in dialyzed children.

Dialysis Adequacy

One of the important reasons that children on dialysis still have a very high rate of traditional and CKD-related risk factors and related CV abnormalities is how we approach dialysis adequacy numbers. Unfortunately, achieving recommended Kt/V urea does not necessarily lead to control of the earlier problems. Data from the Centers for Medicare & Medicaid Services End-Stage Renal Disease Clinical Performance Measures (CPM) Project indicate that 89% of patients receiving hemodialysis and 87% of patients receiving peritoneal dialysis achieved the recommended modality-specific Kt/V. Yet, one-third of children had uncontrolled anemia, and almost one-half had low serum albumin. Another study showed that two-thirds of hemodialysis patients using the same database had uncontrolled hypertension and an elevated Ca × P product. These studies, as well as epidemiologic data on cardiac death in both peritoneal dialysis and hemodialysis, clearly indicate that current dialysis adequacy recommendations based on Kt/V urea are not adequate to decrease CVD morbidity in children with ESRD. Unlike in adults, there have been no randomized pediatric studies examining the role of more frequent or nocturnal hemodialysis on cardiac outcomes. However, small single-center studies of frequent or nocturnal dialysis indicate clinically important improvement in children's health, including growth, hypertension, cardiac hypertrophy, and function. Taking

the potential for a longer and possibly more productive life, the benefits of more frequent and longer dialysis treatment might be much more far reaching in children than in older adults.

Hemodiafiltration (HDF) is a newer technique of dialysis that utilizes a combination of diffusive and convective solute transport through a highly permeable membrane, therefore, achieving clearance of middle- and large-molecular-weight solutes, unlike conventional HD. In the Hemodiafiltration, Heart, and Height (3H) pediatric study, a switch from conventional HD to HDF resulted in significant improvement in inflammation, antioxidant capacity, and endothelial risk profile. The 3H study also showed better BP control and less progression of vascular changes (carotid artery IMT) in HDF compared to hemodialysis children.

Recommended Reading

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These current guidelines provide extensive information on different aspects of evaluation and management of hypertension in children.

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Current normative values on LVM in children.

KDIGO clinical practice guideline for lipid management in chronic kidney disease. *Kidney Int Suppl.* 2013;3:259–305.

Update from the 2003 KDOQI. In addition to practical recommendations, the guidelines include review on novel CVD biomarkers.

Weaver DJ, Mitsnefes M. Cardiovascular disease in children and adolescents with chronic kidney disease. *Semin Nephrol.* 2018;38(6):559–569.

Detailed review on the topic; fully referenced.

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Infectious Complications in Children Undergoing Dialysis

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Introduction

Infectious complications are a major cause of morbidity and mortality in children on peritoneal dialysis (PD) and hemodialysis (HD). This chapter reviews the major infectious risks of each modality, proposed preventive strategies, treatment guidelines, and areas for further development.

Peritoneal Dialysis

The infectious complications associated with PD consist of peritonitis, exit-site infections (ESIs), and catheter tunnel infections (TIs). These complications can occur individually or concurrently.

Peritonitis

Peritonitis is the most significant cause of morbidity in children on PD. Peritonitis is the leading cause of hospitalization, termination of PD, and death among chronic PD patients.

Diagnosis

Peritonitis should be suspected whenever a cloudy effluent is present. Fever, abdominal pain, abdominal distention, and vomiting are other commonly seen symptoms that should raise suspicion. In these settings, culture and cell count of PD fluid should be tested. The diagnosis of peritonitis is empirically made in the setting of a PD fluid cell count of 100 white blood cells (WBCs)/mm^3 or more with at least 50% polymorphonuclear cells (PMNs). Since a cell count may show a false-negative result in the absence of an adequate dwell time, the fluid should ideally be collected after at least 2 hours of dwelling. The ideal method for culturing PD fluid is to centrifuge PD fluid (minimum 50 mL) to obtain a sediment, which is incubated on culture media. This method results in the lowest rate of culture-negative peritonitis. Alternatively, PD fluid can be injected into blood culture bottles for incubation.

Epidemiology

The International Pediatric Peritonitis Registry (IPPR), formed by a consortium of 44 dialysis centers across the globe, showed an incidence of 1.4 ± 0.8 peritonitis episodes per patient over a 38-month analysis period from October 2001 to December 2004. The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) registry reported an annualized peritonitis rate of 0.64 episodes per patient year or 1 episode per 18.8 patient months over the 1992 to 2010 period. Data from the SCOPE (Standardizing Care to Improve Outcomes in Pediatric ESRD) collaborative in 2016 showed an annualized peritonitis rate of 0.42 episodes per patient year or 1 episode every 28.57 months.

Risk Factors

Risk factors for peritonitis include younger age, Black race, incontinence, early catheter uses after placement, exit-site suture placement, upward orientation of the catheter tunnel/exit site, presence of a gastrostomy tube (G-tube), exit-site colonization or infection with *Pseudomonas* species, and nasal or exit-site colonization with *Staphylococcus aureus*. Use of plastic rather than titanium catheter adapter is also associated with significantly higher rates of peritonitis. Analysis of SCOPE collaborative outcome data has identified touch contamination, defined as an accidental disconnection, contamination during treatment, or via defective PD equipment, as an independent risk factor for peritonitis. Although some of these risk factors are nonmodifiable, strategies are now being developed to standardize catheter care practices to obtain the best outcomes in PD with the lowest incidence of peritonitis.

Preventive Strategies

Based on data from the approximately 500 episodes of pediatric peritonitis in the IPPR, the International Society of Peritoneal Dialysis (ISPD) published updated pediatric guidelines for management of peritonitis in 2012. Similarly, the SCOPE collaborative has devised three "bundles" related to evidence-based practices for PD care in the areas of catheter insertion, PD training, and follow-up catheter

care. Adherence with the follow-up bundle in SCOPE has been shown to reduce the rate of peritonitis significantly. Annualized peritonitis rates significantly decreased from 0.63 episodes per patient year to 0.42 at 36 months after initiating follow-up bundle use. However, there has been no association between compliance with the insertion and training bundles and the risk for peritonitis.

With regard to the surgical placement of PD catheters, recommendations have been made regarding the type of catheter, surgical technique, and perioperative care. Based on observational studies, ISPD guidelines recommend the use of a coiled double-cuff rather than a single-cuff Tenckhoff catheter inserted in the lateral or downward-facing position. No sutures should be used to anchor the catheter at the exit site because these represent a nidus for infection. A titanium adapter should be placed because plastic adapters were shown to have higher rates of peritonitis. Perioperative intravenous (IV) antibiotic administration at the time of insertion was associated with a decreased rate of early infection. A first-generation cephalosporin to cover skin flora is recommended because of the increased risk of antibiotic resistance with vancomycin.

In the immediate postoperative period, care is taken to avoid risk factors for infection. This includes immobilization of the exit site with a nonocclusive gauze and tape dressing. Dressings should be changed only once weekly under sterile conditions until the exit site is well healed unless the dressing becomes saturated with fluid or visibly dirty. Furthermore, only trained PD nurses should change a PD catheter dressing during this period. Finally, sponge baths should be used until the catheter site is fully healed, avoiding the exit-site area. Ideally, the catheter should not be used for at least 14 days after insertion to allow adequate healing time and reduce risk of early peritonitis.

Training recommendations focus on the need for a 1:1 ratio of PD nurse trainers to patients or family trained. Goals of training include the ability to safely perform all required PD procedures, the ability to recognize contamination and infection, and knowledge of the appropriate responses to these complications. Furthermore, guidelines emphasize the need for written materials to supplement the training process, as well as a posttraining assessment to ensure competency.

Beyond the perioperative period, a sterile technique remains critical in the avoidance of infection. As with all infection prevention strategies, handwashing is a crucial component of preventive care. An initial washing with soap and water is recommended, followed by the use of an alcohol-based gel. Daily or alternate-day dressing changes, the use of an antiseptic cleansing agent, such as chlorhexidine, and the administration of a topical antibiotic ointment, such as mupirocin or gentamicin, have been associated with fewer infections. Gentamicin may be preferable to mupirocin because of its efficacy against *Pseudomonas* species. When breaks in sterile technique are identified during the PD process, prophylactic antibiotics are indicated to minimize the risk of peritonitis. Prophylaxis is indicated for 1 to 3 days via the intraperitoneal (IP) route.

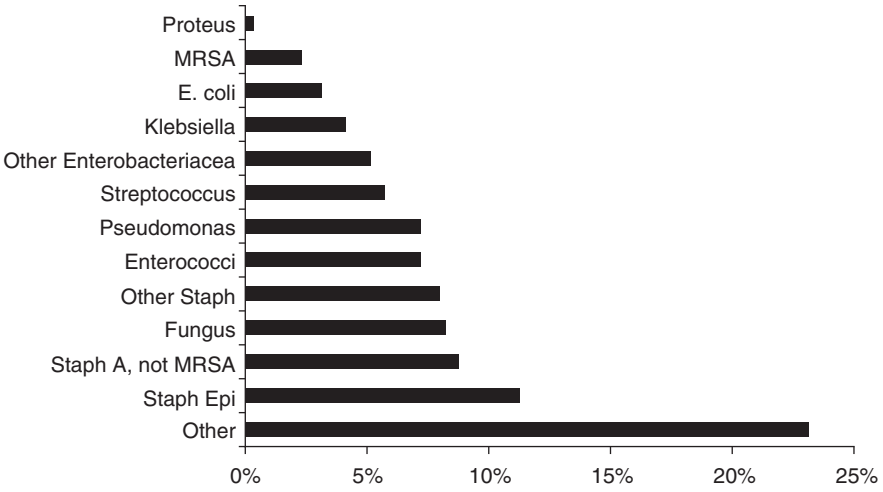
Future procedures represent another point of risk for infection. Therefore, ISPD guidelines recommend prophylactic antibiotics during dental procedures and genitourinary and gastrointestinal surgeries. In addition, the abdomen should be drained of PD fluid before the procedure to reduce the risk of development of peritonitis. In some procedures with high risk of bacterial translocation, withholding PD for 1 to 2 days, if possible, may be beneficial.

G-tube placement represents a significant source of concern because it is associated with higher rates of peritonitis and is frequently needed in PD patients to assist in appropriate nutrition. If possible, G-tube placement should be performed before or at the time of PD catheter placement. If a G-tube is placed after PD has been instituted, the open surgical technique is preferable over the laparoscopic approach because it enables immediate suturing of the stomach to the abdominal wall, minimizing the amount of gastric leakage. Appropriate antibiotic prophylaxis should be given, and PD should be withheld for at least 1 day. Antifungal prophylaxis is also indicated because of an observed increased risk of fungal peritonitis with G-tube placement.

Microbiology

Causative pathogens of peritonitis vary extensively by locale. Analysis from the IPPR showed that whereas Gram-positive peritonitis is more common in Europe, *Pseudomonas* species were eight times more common in the United States. Furthermore, in North America, culture-negative peritonitis accounted for 11% of episodes, but in Mexico, it accounted for 67%. Geographic differences are thought to be due to both environmental factors as well as differences in regional practices regarding chronic catheter care.

Currently, there seems to be a general trend toward fewer Gram-positive infections overall. This may be due to improvement in technique, as well as the implementation of *S. aureus* colonization eradication regimens. In 1990, a European study by Schaefer et al. showed that approximately 65% of peritonitis cases were Gram-positive, and 20% of cases were Gram-negative. IPPR data from 2007 showed that in the United States, approximately 45% of peritonitis cases were Gram-positive, and 40% were Gram-negative. SCOPE collaborative analysis from 2016, using a large sample size, showed that approximately 40% of peritonitis cases were Gram-positive, 20% were Gram-negative, and 10% were polymicrobial. The most common Gram-positive isolates from both IPPR and SCOPE collaborative data were coagulase-negative staphylococci followed by *S. aureus*. The most common Gram-negative isolates from both IPPR and SCOPE collaborative data were *Pseudomonas* species, followed by *Klebsiella*. Fig 86.1, taken from a SCOPE collaborative analysis, shows the rates of different causative organisms. Fungal infections represent another important source of peritonitis, ranging from 3% to 9% of all cases, and typically have a more severe course.



• **Fig. 86.1** Organisms cultured from patients with peritonitis. Gram-positive organisms were the predominant bacteria in peritonitis (*n* = 389 cultures; missing two cultures; may have more than one pathogen per peritonitis episode). *E. coli*, *Escherichia coli*; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *Staph*, *Staphylococcus*; *Staph A*, *Staphylococcus aureus*; *Staph Epi*, *Staphylococcus epidermidis*. (From Sethna CB, Bryant K, Munshi R, et al. Risk factors for and outcomes of catheter-associated peritonitis in children: the SCOPE collaborative. *Clin J Am Soc Nephrol*. 2016;11(9):1590-1596.)

Treatment

Bacterial Peritonitis

IP antibiotic administration represents the mainstay of management for peritonitis. IP administration achieves a rapid, high concentration of drug levels at the site of infection, and absorption from the peritoneal cavity generally results in therapeutic blood levels as well. Most antibiotics are administered continuously, given as a constant dose per liter injected into the dialysate, with the subsequent total amount received dependent on the patient's dialysis prescription. Based on the pharmacokinetic profiles of various antibiotic agents, as well as the patient's residual renal function, dosing can sometimes be done intermittently rather than continuously. In these cases, drug levels should be checked to determine a redosing schedule. Table 86.1 shows the commonly used antibiotics and their recommended dosing.

Empiric treatment should begin with both Gram-positive and Gram-negative coverage and should be adjusted accordingly based on culture results. Cefepime has adequate coverage of both Gram-positive and Gram-negative organisms and is recommended as first-line treatment. Alternatively, a first-generation cephalosporin plus ceftazidime (a third-generation cephalosporin) or an aminoglycoside can be used in combination. In patients with a history of methicillin-resistant *S. aureus* (MRSA) or centers with high rates of MRSA (> 10% of all *S. aureus* infections), vancomycin should be started empirically with any regimen pending culture results. Figs. 86.2 and 86.3 show recommended treatment strategies based on culture results.

The duration of antibiotic treatment for peritonitis depends on the organism isolated and severity of the infection. For coagulase-negative staphylococci and *Streptococcus* species, a 2-week course of treatment is considered sufficient. *S. aureus* peritonitis is frequently more severe, so a 3-week course is recommended. *Enterococcus* species, although it usually causes a mild infection, is typically treated for 2 to 3 weeks because the initial empiric treatment often does not cover the bacteria. In settings of Gram-negative peritonitis other than *Pseudomonas* species, the treatment regimen is generally 2 weeks. However, in cases of *Pseudomonas* species or other extended-spectrum β-lactamase (ESBL)–producing species, a 3-week course is recommended. *Pseudomonas* species can create a biofilm within the catheter lumen, increasing the risk of treatment failure. For that reason, the addition of an aminoglycoside to the treatment regimen is recommended for synergy.

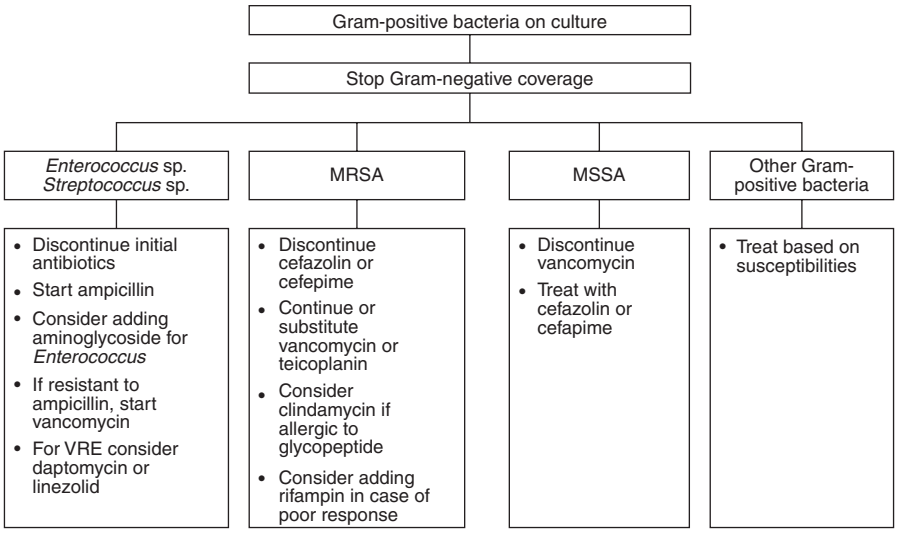
Fungal Peritonitis

In most cases, fungal peritonitis is preceded by bacterial infection and antibiotic use. Munshi et al., using SCOPE collaborative data, showed that although most cases of fungal peritonitis were associated with recent antibiotic exposure, only 17% of cases followed the antibiotic treatment of peritonitis. Fungal peritonitis is frequently more severe than that caused by bacterial infection, with higher rates of associated catheter loss, membrane failure, and mortality. Multiple studies in the adult population examining the use of prophylactic antifungal administration at the time of antibiotic use demonstrated lower rates of fungal peritonitis in those who received prophylaxis. Therefore, prophylaxis with either nystatin or fluconazole is recommended at times of antibiotic therapy. If a fungal peritonitis occurs, the ISPD recommends early catheter removal, with treatment for 2 weeks or longer after complete clinical resolution has been achieved. Early catheter removal has been shown to decrease the risk of peritoneal membrane failure. A minimum of 2 to 3 weeks is suggested before placement of a new catheter, necessitating a temporary switch in modality to HD. Antifungal treatment is generally with systemic fluconazole.

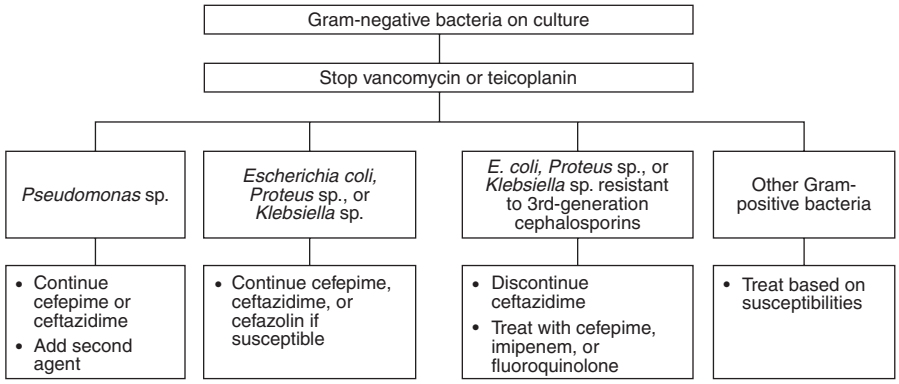
TABLE 86.1 Pharmacologic Agents and Dosing Regimens for Treatment of Peritonitis

Antibiotic Dosing Recommendations for the Treatment of Peritonitis			
	Therapy Type		
	Continuous*		
Antibiotic Type	Loading Dose	Maintenance Dose	Intermittent*
Aminoglycosides (IP)†			
Gentamicin	8 mg/L	4 mg/L	—
Netilmicin	8 mg/L	4 mg/L	Anuric: 0.6 mg/kg
Tobramycin	8 mg/L	4 mg/L	Non-anuric: 0.75 mg/kg
Amikacin	25 mg/L	12 mg/L	—
Cephalosporins (IP)			
Cefazolin	500 mg/L	125 mg/L	20 mg/kg
Cefepime	500 mg/L	125 mg/L	15 mg/kg
Cefotaxime	500 mg/L	250 mg/L	30 mg/kg
Ceftazidime	500 mg/L	125 mg/L	20 mg/kg
Glycopeptides (IP)‡			
Vancomycin	1000 mg/L	25 mg/L	30 mg/kg; Repeat dosing: 15 mg/kg every 3–5 days
Teicoplanin§	400 mg/L	20 mg/L	15 mg/kg every 5–7 days
Penicillins (IP)†			
Ampicillin	—	125 mg/L	—
Quinolones (IP)			
Ciprofloxacin	50 mg/L	25 mg/L	—
Others			
Aztreonam (IP)	1000 mg/L	250 mg/L	—
Clindamycin (IP	300 mg/L	150 mg/L	—
Imipenem-cilastin (IP)	250 mg/L	50 mg/L	—
Linezolid (PO)	Age < 5 years: 30 mg/kg/day divided into three doses Age 5–11 years: 20 mg/kg/day divided into two doses Age ≥ 12 years: 600 mg/dose twice daily		—
Metronidazole (PO)	30 mg/kg/day divided into three doses (maximum, 1.2 g/day)		—
Rifampin (PO)	10–20 mg/kg/day divided into two doses (maximum, 600 mg/day)		—
Antifungals			
Fluconazole (IP, IV, or PO)	6–12 mg/kg every 24–48 h (maximum, 400 mg/day)		—
Caspofungin (IV only)	70 mg/m^2 on day 1 (maximum, 70 mg/day)	50 mg/m^2/day (maximum, 50 mg/day)	—

* For continuous therapy, the exchange with the loading dose should dwell for 3 to 6 hours; all subsequent exchanges during the treatment course should contain the maintenance dose. For intermittent therapy, the dose should be applied once daily in the long dwell unless otherwise specified.
† Aminoglycosides and penicillins should not be mixed in dialysis fluid because of the potential for inactivation.
‡ In patients with residual renal function, glycopeptide elimination may be accelerated. If intermittent therapy is used in such a setting, the second dose should be time based on a blood level obtained 2 to 4 days after the initial dose. Redosing should occur when the blood level is below 15 mg/L for vancomycin, or below 8 mg/L for teicoplanin. Intermittent therapy is not recommended for patients with residual renal function unless serum levels of the drug can be monitored in a timely manner.
§ Teicoplanin is not currently available in the United States.
IP, Intraperitoneal; *IV*, intravenous; *PO*, oral.
From Warady BA, Bakkaloglu S, Newland J, et al. Consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving peritoneal dialysis: 2012 update. *Perit Dial Int.* 2012;32(suppl):S29-S86.



• **Fig. 86.2** Treatment strategy for Gram-positive peritonitis. *MRSA*, methicillin-resistant *Staphylococcus aureus*; *MSSA*, methicillin-sensitive *Staphylococcus aureus*; *VRE*, vancomycin-resistant enterococcus. (From Warady BA, Bakkaloglu S, Newland J, et al. Consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving peritoneal dialysis: 2012 update. *Perit Dial Int.* 2012;32(suppl):S29-S86.)



• **Fig. 86.3** Treatment strategy for Gram-negative peritonitis.

Culture-Negative Peritonitis

Culture-negative peritonitis represents another management challenge. IPPR data showed that in the United States, 11% of peritonitis cases were culture-negative, while SCOPE collaborative analysis showed that 25% of peritonitis cases were culture-negative. The ISPD 2012 guidelines recommend continuing empiric coverage for 2 weeks in these settings. Although the IPPR reported very high rates of clinical improvement after 72 hours of treatment in culture-negative peritonitis, when improvement does not occur, patients should be cultured again, and consideration of catheter removal should be made. Centers that have > 20% culture-negative rates should be encouraged to review their culture techniques with staff.

Adjunct Therapies

In addition to appropriate antimicrobial therapy, adjunctive treatments may be useful in the management of peritonitis. There is evidence to suggest that heparin added to the dialysate during peritonitis may have a beneficial effect on treatment outcomes and catheter patency. This is due to the anticoagulant and anti-inflammatory properties of heparin. Other strategies to improve outcomes include reduction of dwell volumes for pain management and prolongation of dialysate dwell times to optimize the peritoneal milieu for bactericidal activity.

Refractory and Relapsing Peritonitis

Refractory peritonitis is defined as lack of symptom resolution after 5 days of appropriate antibiotics. This is frequently seen in the setting of concomitant tunnel infections. In these cases, catheter removal is recommended as part of management with a waiting period of 2 to 3 weeks before a new catheter is placed.

Relapsing peritonitis is defined as recurrence of peritonitis with the same organism within 4 weeks of antibiotic completion for the initial episode or, alternatively, two culture-negative episodes within 4 weeks. It occurs in approximately 10% to 20% of all episodes. Treatment should follow standard recommendations for peritonitis management; however, duration should be lengthened to 3 weeks regardless of the isolated organism. In addition,

fibrinolytics are recommended to break up any biofilms or clots that may be present in the catheter lumen. Catheter removal with immediate replacement with a new catheter may be possible depending on the organism isolated.

Posttreatment Care

After an episode of peritonitis, ISPD guidelines recommend retraining PD providers and a home visit to identify the root cause of the infection.

Peritoneal Dialysis Catheter-Related Infections

Catheter-related infections consist of ESIs and TIs.

Diagnosis

The diagnosis of ESI is made on the basis of a scoring system proposed by Schaefer et al. (Table 86.2), taking into account the presence of swelling, redness, crusting, pain, and secretions, with or without the isolation of a pathogenic organism. A score of 2 or higher, along with a positive exit-site culture or four or more without a culture, is considered diagnostic. TIs usually present with redness, tenderness, and edema along the subcutaneous part of the catheter with or without drainage.

Epidemiology

Catheter TIs or ESIs may occur alone or in conjunction with peritonitis. According to SCOPE collaborative analysis, the annualized rate of catheter-related infections (ESIs and TIs separately or in combination) is 0.25 per year of PD. Of all catheter-related infections, 69% were ESIs only, 23% were TIs only, and 8% were a combination of ESIs and TIs.

Risk Factors

As with peritonitis, risk factors for catheter-related infections include catheter cuff extrusion, catheter traction injuries, exit-site colonization, or infection with *Pseudomonas* species, and nasal or exit-site colonization with *S. aureus*. According to SCOPE collaborative analysis, age less than 2 years old is associated with fewer catheter-related infections, while age 6 to 12 years old is associated with more catheter-related infections. The presence of G-tube, vesicostomy, or other stoma did not significantly increase risk of ESIs and TIs. Worse adherence to both SCOPE training and follow-up bundles, as described previously, were associated with increased catheter-related infection.

TABLE 86.2 Exit-Site Scoring System for Infection

	0	1	2
Swelling	None	Exit site only (<0.5 cm)	Including part or all of the tunnel
Crust	None	<0.5 cm	>0.5 cm
Redness	None	<0.5 cm	>0.5 cm
Pain on pressure	None	Slight	Severe
Secretion	None	Serous	Purulent

From Schaefer F, Kaus G, Muller-Wiefel DE, et al. Intermittent versus continuous intraperitoneal glycopeptide/ceftazidime treatment in children with peritoneal dialysis-associated peritonitis. The Mid-European Pediatric Peritoneal Dialysis Study Group (MEPPS). *J Am Soc Nephrol.* 1999;10:36-145.

TABLE 86.3 Antibiotic Dosing Guidelines for Patients on Hemodialysis

Empirical dosing pending culture results

Vancomycin plus empirical Gram-negative rod coverage based on local antibiogram data

OR

Vancomycin plus gentamicin

(Cefazolin may be used in place of vancomycin in units with a low prevalence of methicillin-resistant staphylococci)

Vancomycin: 20-mg/kg loading dose infused during the last hour of the dialysis session and then 500 during the last 30 minutes of each subsequent dialysis session

Gentamicin (or tobramycin): 1 mg/kg, not to exceed 100 mg after each dialysis session

Ceftazidime: 1 g IV after each dialysis session

Cefazolin: 20 mg/kg IV after each dialysis session

For *Candida* infection:

An echinocandin (caspofungin 70-mg IV loading dose followed by 50 mg IV daily; micafungin 100 mg IV daily; or anidulafungin 200-mg IV loading dose followed by 100 mg IV daily); fluconazole (200 mg orally daily); or amphotericin-B

IV, *Intravenous*.
From Mermel LA, Allon, M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Disease Society of America. *Clin Infect Dis.* 2009;49(1):1-45.

Preventative Strategies

As poor adherence to SCOPE training and follow-up bundles is associated with increased catheter-related infection, good adherence to these bundles will help prevent catheter-related infections. Other strategies include daily or alternate-day dressing changes, the use of an antiseptic cleansing agent such as chlorhexidine, and administration of a topical antibiotic ointment. Gentamicin may be preferable to mupirocin because of its efficacy against *Pseudomonas* species.

Microbiology

S. aureus and *Pseudomonas* species represent the most common causes of TI/ESIs. Since the introduction of mupirocin prophylaxis, *Pseudomonas* species represent the most common cause of combined catheter-related infection and peritonitis.

TABLE 86.4 Antibiotic Lock Dosing for Hemodialysis Catheter Infections*

Antibiotic and Dosage	Heparin or Saline, IU/mL
Vancomycin, 2.5 mg/mL	2500 or 5000
Vancomycin, 2.0 mg/mL	10
Vancomycin 5.0 mg/mL†	0 or 5000
Ceftazidime, 0.5 mg/mL	100
Cefazolin, 5.0 mg/mL	2500 or 5000
Ciprofloxacin, 0.2 mg/mL‡	5000
Gentamicin, 1.0 mg/mL	2500
Ampicillin, 10.0 mg/mL	10 or 5000
Ethanol, 70%§	0

* These antibiotic lock solutions will not precipitate at the given concentrations. Cefazolin is the preferred agent for treatment of methicillin-susceptible staphylococci, and vancomycin is the preferred agent for treatment of methicillin-resistant staphylococci. Ceftazidime, gentamicin, or ciprofloxacin can be used for treatment of Gram-negative microorganisms. Ampicillin is the preferred agent for infections caused by ampicillin-sensitive enterococci, and vancomycin is the preferred agent for treatment of ampicillin-resistant enterococci other than vancomycin-resistant enterococci. The use of an ethanol lock can be considered for the treatment of a mixed Gram-positive and Gram-negative infection.

† Vancomycin at 5 mg/mL is more efficacious than at 1 mg/mL in eradicating staphylococci embedded within biofilm. A precipitate appears when mixing 10 mg/mL of vancomycin with 10,000 IU/mL of heparin; however, by agitating the solution for ~10 seconds, the precipitation resolves and the solution remains precipitate free for 72 hours at 37°C. The lock solution in 2500 IU/mL heparin can be made as follows: Using vials containing 50 mg/mL of vancomycin in water, remove 2 mL and dilute in 8 mL 0.9% NaCl, resulting in 10 mg/mL of vancomycin. Place 1 mL of 5000 IU/mL heparin in a glass test tube and mix with 1 mL of the 10-mg/mL vancomycin solution.

‡ The maximum concentration of ciprofloxacin is limited because of precipitation at higher concentrations.

§ An in vitro study demonstrated the compatibility of ethanol 70% and silicone or polyether urethane catheters.

From Mermel LA, Allon, M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Disease Society of America. *Clin Infect Dis.* 2009;49(1):1-45.

Treatment

For ESIs, oral antibiotic treatment is generally acceptable. For TIs, treatment can be oral, IV, or IP. Treatment duration is generally 2 to 4 weeks and for at least 7 days after resolution of external symptoms. First-generation cephalosporins or ciprofloxacin (which has anti-Pseudomonal activity) are recommended as empiric oral treatment, pending culture results. TI or ESI in the presence of peritonitis is considered a definitive indication for catheter removal with replacement after 2 to 3 weeks catheter-free. On the other hand, repeatedly relapsing or refractory ESI or TI catheters may be removed and immediately replaced.

Hemodialysis

Most children receiving HD do so using a central venous catheter (CVC). Although arteriovenous fistulas (AVFs) and arteriovenous grafts (AVGs) are feasible and preferred in children, in part because of a significantly lower infection rate, they are underused because of a variety of factors, including patient size, lack of personnel skilled in microsurgical technique, and expectation of an expedited kidney transplant. The use of CVC for HD places patients at risk for catheter-associated bloodstream infections (CABSIs) as well as catheter-related infections, including ESIs and TIs. CABSIs, TIs, and ESIs may occur alone or together.

Bloodstream Infections

Diagnosis

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) defines a CABSI as the same organism growing from a peripheral blood culture and catheter segment culture with clinical manifestations of infection such as fever or chills and no other apparent source of infection.

Epidemiology

In multiple studies, the average rate of CABSIs in children is 1.3 to 10.1 episodes per 1000 catheter days (or 3.9 to 30.3 episodes per 100 patient months). The average rate of CABSIs leading to catheter failure is 1.1 to 1.3 episodes per 1000 catheter days (or 3.3 to 3.9 episodes per 100 patient months).

Risk Factors

Risk factors for CABSIs include young age, colonization with *S. aureus*, multiple previous CABSIs and catheter-related infections, elevated ferritin levels, hypoalbuminemia, immunosuppression, diabetes mellitus, poor catheter hygiene, and high frequency of catheter manipulation. Tunneled cuffed catheters are associated with lower infection risk than temporary catheters. Interestingly, femoral catheters have been shown in more than one study to have infection rates similar to nonfemoral catheters. Although subclavian catheters have shown lower rates of infection, they are often not used because of the risk of stenosis.

Preventive Strategies

In alignment with the practices recommended by the Centers for Disease Control and Prevention (CDC), the SCOPE collaborative has devised five "bundles" related to evidence-based practices for HD care in the areas of exit-site assessment, catheter connection procedure, catheter disconnection procedure, cap care procedure, and exit-site care. Adherence to these bundles has been shown to reduce the rate of CABSIs significantly.

Catheters should be managed only by trained dialysis nurses. When connecting or disconnecting an HD catheter or performing dressing change procedures, proper hand hygiene must be used along with personal protective equipment. In addition, the patient must wear a mask. Hubs and

caps must be disinfected when connecting or disconnecting an HD catheter, and caps must be changed regularly based on manufacturer recommendations. ClearGuard HD antimicrobial barrier caps (chlorhexidine-coated barrier caps) have been shown to reduce CABSI in some studies.

The HD catheter site should be visually assessed through a transparent dressing daily for signs and symptoms of infection. The dressing, catheter, and caps must be kept dry. Some recommend catheter dressing changes with every dialysis session, but others use once-weekly regimens. When performing dressing changes, antiseptic must be applied to the exit site and allowed to dry. Small studies have demonstrated a lower incidence of CABSIs in patients using chlorhexidine for exit-site care as opposed to povidone-iodine; therefore, chlorhexidine should be used for exit-site care. Catheter exit sites must be covered in a sterile fashion and are not allowed to get wet between catheter dressing changes. Ideally, a dressing should be used that allows easy visualization of the exit site without removal of the dressing. There is some evidence to support the use of chlorhexidine-impregnated dressings in reducing catheter-related infections. These dressings are also described as an alternative to exit-site antimicrobial ointment, which can lead to catheter compatibility issues.

Prophylactic topical antibiotics and use of antibiotic catheter lock solutions are not routinely recommended because of the risk of inducing resistant strains of bacteria. However, heparin locks, which have both anticoagulant and antimicrobial activity, are recommended, and reduce the risk of clot formation and infection. The European Society for Paediatric Nephrology Dialysis Working Group recommends using tissue plasminogen activator (t-PA) locks rather than heparin locks as it has been shown to reduce risk of clot and infection further; however, t-PA locks are not widely used in North America due to increased risk of bleeding and increased expense.

Microbiology

According to the SCOPE collaborative, approximately 50% of CABSI cases were caused by Gram-positive organisms, 30% were caused by Gram-negative organisms, 20% were polymicrobial, and only 2% were fungal in origin. The most commonly isolated bacteria in CABSIs are *S. aureus* and coagulase-negative staphylococci such as *Staphylococcus epidermidis*.

Treatment

CABSIs require IV antibiotics with initial empiric treatment with either vancomycin or cefazolin (depending on risk of MRSA), as well as Gram-negative bacilli coverage based on the local antibiogram (third- or fourth-generation cephalosporin, carbapenem, or β-lactam/β-lactamase combination) is recommended pending culture results. Broader empiric coverage for *Pseudomonas* species and fungi may be considered in high-risk patients. Antibiotics should be administered through the catheter or, alternatively, through a peripheral vein along with antibiotic locks to the catheter. Antibiotics should also be guided by the local infection rates, antibiotic sensitivities, and dialysis center policies. Tables 86.3 and 86.4 show antibiotic guidelines for patients on HD.

Per KDIGO, the treatment of CABSIs differs depending on multiple factors. If fever and bacteremia or fungemia do not resolve within 2–3 days of initiation of antibiotics, the catheter should be urgently removed with temporary nontunneled catheter placement, and appropriate antibiotics or antifungals should be administered for 4 to 6 weeks. If there are no other access options, the catheter may be exchanged over a guidewire. Alternatively, the catheter can be salvaged with the use of antibiotic locks along with systemic antibiotics. Of note, the date of the first negative culture is considered the first day of antibiotic treatment.

If fever and bacteremia or fungemia resolve within 2–3 days of initiation of antibiotics, treatment depends on the organism isolated. For infections with coagulase-negative staphylococci, Gram-negative bacilli, or *Candida* species, appropriate antibiotics or antifungals should be administered for 14 days. For infections with *S. aureus*, appropriate antibiotics should be administered for 4 weeks. For infections due to *S. aureus*, *Pseudomonas aeruginosa*, fungi, or mycobacteria, KDIGO recommends catheter removal with temporary nontunneled catheter placement. If the infection is caused by a different organism or if there are no other access options, the catheter may be exchanged over a guidewire. Alternatively, the catheter can be salvaged with use of antibiotic locks along with systemic antibiotics. Fig. 86.4 summarizes recommended treatment strategies.

Hemodialysis Catheter-Related Infections

Catheter-related infections consist of ESIs and TIs.

Diagnosis

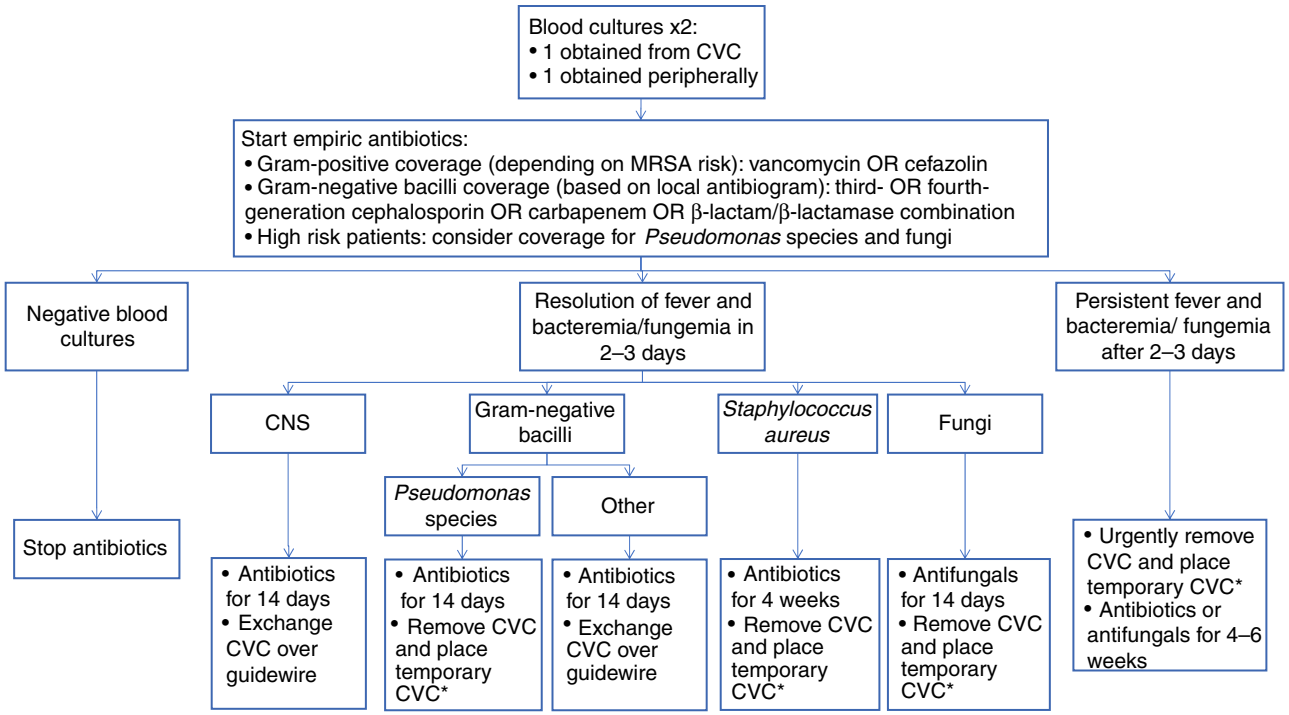
TIs are defined as inflammation (hyperemia, induration, and/or tenderness) along the subcutaneous tunnel beyond 2 cm from the exit site. ESIs are defined as inflammation (hyperemia, induration, and/or tenderness) confined to the area surrounding the exit site within 2 cm.

Epidemiology

The average rate of ESI or TI is 6.9 to 9.6 episodes per 1000 catheter days (or 20.7 to 28.8 episodes per 100 patient months). KDOQI recommends that if ESIs or TIs are associated with drainage, the drainage should be collected and cultured.

Risk Factors

There is not an abundance of data on risk factors for catheter-related infections. Some studies have concluded that risk factors include colonization with *S. aureus*, multiple previous catheter-related infections, diabetes mellitus, poor catheter hygiene, and a high frequency of catheter manipulation. Tunneled cuffed catheters are associated with lower infection risk than temporary catheters.



* If there are no other access options, exchage CVC over a guidewire or salvage CVC with antibiotics locks

• **Fig. 86.4** Treatment algorithm for CVC-related infection. *CVC*, Central venous catheter; *CNS*, coagulase negative staphylococcus. (Adapted from Lok, CE, Huber TS, Lee T, et al. KDOQI Vascular Access Guideline Work Group. KDOQI clinical practice guideline for vascular access: 2019 update. *Am J Kidney Dis*. 2020;75(4)(suppl 2):S1-S164.)

Preventive Strategies

Prevention strategies are discussed in the "Bloodstream Infection" section on "Prevention."

Microbiology

There is little data regarding catheter-related infection microbiology. The most commonly isolated bacteria in ESIs and TIs are coagulase-negative staphylococci. According to some, *S. aureus* is the second most common, but according to others, *Pseudomonas* species are second most common.

Treatment

ESIs can generally be treated with topical antibiotics that cover Gram-positive organisms, including MRSA, for 7 to 14 days; mupirocin ointment is a viable option. On the other hand, like CABSIs, TIs require IV antibiotics. Initial empiric treatment with either vancomycin or cefazolin (depending on risk of MRSA) as well as Gram-negative bacilli coverage based on the local antibiogram (third- or fourth-generation cephalosporin, carbapenem, or β-lactam/β-lactamase combination) is recommended pending culture results. Broader empiric coverage for *Pseudomonas* species and fungi may be considered in high-risk patients. Antibiotics should be administered through the catheter or, alternatively, through a peripheral vein along with antibiotic locks to the catheter.

The duration of treatment for TIs is generally considered sufficient with 10 to 14 days of appropriate antibiotics. If the TI is not effectively treated with antibiotics, KDOQI recommends considering catheter exchange with a new subcutaneous tunnel to preserve the venous access site. Alternatively, if this is not possible, the catheter should be removed with a new catheter placed at a new entry site.

Future Steps

The continued use of databases and registries to collect information on HD- and PD-related infections is needed. The results of these must be continuously analyzed to devise appropriate guidelines regarding catheter care for prevention of infection. On a local level, hospitals should be encouraged to create antibiograms of catheter-related infections to implement the most appropriate treatment regimens while minimizing the risk of further antimicrobial resistance. Finally, a stronger push for AVF placement in children on chronic HD is recommended to reduce rates of catheter-related infections.

Recommended Reading

The EMMES Corporation. *North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS); 2011. Annual Dialysis Report*.

2011 report from a large database of U.S. pediatric dialysis patients encompassing many aspects of HD and PD care.

Keswani M, Redpath Mahon AC, Richardson T, et al. Risk factors for early onset peritonitis: the SCOPE collaborative. *Pediatr Nephrol.* 2019;34(8):1387–1394.

Discusses early PD catheter use as a risk factor for early peritonitis.

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87

Caring for the Teenager in an Adult Unit

CLAIRE DUNPHY, PhD • RACHEL A. ANNUNZIATO, PhD

Overview of Transition/Transfer to Adult Care

Adolescence is known as a period of transition toward adulthood that is characterized by significant developmental changes in cognitive, emotional, and social domains. For adolescent/young adult dialysis patients, this process also involves the acquisition of self-managed medical care. For many patients, this time is also marked by treatment nonadherence, lapses in medical care, and poor outcomes. As this transition progresses, patients must transfer from pediatric care to an adult treatment setting at some specific point. This change represents a distinct shift from supervisory, child-centered care to self-directed treatment, thus, moving from a more dependent to independent role. The exact timing of transfer often varies based on patient- and site-specific factors, and therefore, offering a standardized approach is challenging. This chapter provides a review of issues relevant to the management of teenage and young adult dialysis patients receiving care in the adult nephrology setting. Recent empirically supported approaches to addressing transition and transfer of care are presented, followed by a discussion of functional outcomes during this time. Other special considerations for this patient population, including perspectives of transitioning patients and families and other posttransfer recommendations, are also reviewed.

Transitional Procedures for Pediatric Dialysis Patients

Guidelines established by the International Society of Nephrology/International Pediatric Nephrology Association state that preparational efforts should be made to help support patients prior to the transfer of care from pediatric to adult settings. However, there is a great deal of variation across dialysis centers in specific transitional procedures. For example, there is no standardized time of transfer; patients may be transferred from pediatric to adult care anytime between ages 16 and 26 years. Some sites have strict guidelines dictating when patients transfer, while others take a more individualized approach to the process. Specific procedures may be influenced by local rules and regulations.

The importance of preparing patients for transition well before the transfer process is initiated and widely recognized. This preparatory approach may involve encouraging patients to begin assuming a greater role over their health care early in adolescence. However, adolescence is known to be a high-risk period for nonadherence. At the same time, as patients are getting ready to leave pediatrics, they may be extremely vulnerable to disruptions in their health care management. Indeed, a seminal paper by Watson described a sample of 20 transferring renal transplant recipients. Over a 36-month follow-up period, seven patients (35%) lost their graft. It appeared that patients struggled with shifting to a new care team and managing their health care responsibilities, such as medication taking and appointment attendance, independently during this time. An abundance of data supports the relationship between the transitional time period, nonadherence, and poor outcomes such as graft loss.

The results of a 2006 survey conducted by Bell of 58 pediatric dialysis centers in North America and Europe highlighted a number of specific problem points for transferring patients. One concern is the relative lack of dedicated transition programs. Only one-third of the responding centers reported having a transition program but most expressed a need for one. This finding has persisted over time. A more recent survey of 49 nephrology centers in the United States indicated that only 23% had a transition clinic in place. Similarly, a study of centers in Japan found that just 4 of 101 centers had a formal transition program. In the Bell study, respondents were also asked if their adult care counterparts had support in place for patients exhibiting nonadherence; this was the case for only 26% of the centers. However, some elements of preparation appeared stronger. For example, most sites reported that their patients were able to visit and choose their adult dialysis center before transferring. The majority of sites also reported that resources were available to assist transferring patients with navigating changes in insurance benefits. Self-management was assessed as well.

Fewer than 20% of respondents reported that their adolescent patients were self-managing their care as measured by making appointments and filling prescriptions autonomously at least 60% of the time, although patients' mastery of PD administration was better (48% could do so 60% of the time). Data also suggest that validated assessment tools are inconsistently used by providers to assess readiness to transition.

As highlighted by these data, several distinct challenges may emerge during the transfer process. These include systematic patient and family barriers to a smooth, successful transfer. At the systematic level, there are issues specific to each service as well as general considerations. On the pediatric side, scarce resources or inattention to transition or transfer may lead to poor planning and preparation. These concerns are faced on the adult side as well; staff may be less accustomed and equipped to meet the special needs of adolescent or young adult patients. Overall, there may be a lack of communication and coordination between pediatric and adult units, which certainly disrupts this process. Patients may be resistant to leaving familiar, trusted providers, a sentiment that is often echoed by family members as well. In the face of such challenges, patients may not be able to form connections with their new providers easily, and this could translate into disengagement and nonadherence.

Patient Perspectives on Transfer

A substantial body of literature focused on the perspectives of transferring patients and their families have emerged in response to an increasing focus on transition-related issues. A recent systematic review analyzed 11 studies exploring the experiences of adolescent patients, their families, and medical providers with the transfer to adult nephrology care. Themes of preparedness to transfer to adult care, emotional attachment to the pediatric care team, adjustment to the adult care setting, and adolescent self-care were identified in the literature. Of note, self-reported preparedness at the time of transfer ranged widely, with 20% to 80% of adolescents feeling prepared across studies. This indicates that while some adolescents may enter the adult setting feeling quite ready for this shift, others may feel ill-prepared even as the transfer is imminent. This review also found that transferring patients endorse a higher degree of comfort with their familiar pediatric providers and more difficulty discussing issues like treatment nonadherence with the adult care team. This dynamic may be a barrier to detecting nonadherence posttransfer. Patients across several studies also endorsed difficulty adjusting to the new treatment setting in light of differences in aspects of the physical environment, as well as new personnel and processes, shorter length of appointment times, and perceived differences in interactions with providers. For example, one area of concern is related to parent involvement: in the adult setting, parents may be excluded from care discussions. This shift may be challenging or even unwelcome for patients who are accustomed to substantial parental involvement in medical treatment. Still, it appears that some transferring patients enthusiastically embrace the increase in independence they experience in the adult setting. These findings are consistent with clinical data and observations that some patients struggle to engage with treatment after a transfer, while others transfer quite successfully.

Evidence-Based Strategies for Optimizing Transfer

Given these modifiable barriers to a successful transition and transfer, many solutions have been proposed. Programs to support transitioning patients often take the form of a specialized, multidisciplinary transition clinic bridging the gap between pediatric and adult services, although peer-mentoring programs and other more process-driven interventions have also been explored. The literature on the transition to adulthood and specifically the actual transfer part of this overall process has long been limited by minimal data to inform interventions, although this is beginning to change. According to a June 2014 technical brief by the Agency for Healthcare Research and Quality (AHRQ), a handful of studies describe data-driven approaches to improving transfer in end-stage organ failure patients. To date, no studies have focused yet on dialysis patients specifically. Although the studies detailed by the AHRQ brief have been specific to transplant recipients, important lessons can be derived from them. On a larger scale, these data suggest the utility of transition clinics for ESRD patients. Some caution should be exercised in interpreting findings because these studies have all been retrospective without random assignment to control conditions; nonetheless, results are promising.

The AHRQ described three studies that supported the use of transition clinics. In one study, outcomes for renal transplant recipients seen in a transition clinic ($n = 12$) were compared with a historical control group, pretransition clinic ($n = 34$). Patients were treated in the transition clinic every 4 to 6 months until transfer while also being seen in the pediatric transplant clinic. During this time, patients had access to a range of team members (a pediatric nephrologist, renal nurse, youth health specialist, renal pharmacist, renal dietitian, and social worker). The transition clinic emphasized several self-management goals, including identifying a primary care provider, demonstrating medication knowledge, recognizing signs of rejection and infection, appraisal of ability to self-manage, and awareness of reproductive health issues. Outcomes were compared between the groups for a 2-year period after transfer. In the pretransition group, 24% of patients either died or lost their graft and had to begin dialysis versus none in the transition clinic group. Cost estimates suggested similar expenditures between the two groups but substantial additional costs because of induction of dialysis and death in the historical controls.

Two other studies reviewed by the AHRQ described transition clinics with additional services. In the first study, an

integrated pediatric and young adult joint transition clinic and care pathway was established for pediatric nephrology patients in two London hospitals. Patients were seen jointly by pediatric and adult teams from 15 to 18 years of age in preparation for transfer at the age of 18 years. Additionally, a young adult clinic was established within the adult unit and later at a student college and sports center to encourage peer interaction among patients. The first group of nine patients had transferred before the implemented transition program, and a second group of 12 patients received the revamped services. Data on acute organ rejection, morbidity, and hospital admissions were collected between 1 and 60 months after transfer. Results indicated that six transplants were lost in the earlier group (67%), but no transplant losses were observed in the second group. The second study of 66 pediatric kidney transplant patients compared three different transition models offered. The first approach, model 1 (n = 26), was a young adult clinic led by a specialized adult nephrologist. Model 2 (n = 15) involved a phase of alternate appointments with an adult nephrologist in private practice over 1 to 2 years before transfer in conjunction with three yearly visits to the adult transplant clinic within the university hospital. Model 3 (n = 25) was the same as model 2, minus the connection to the adult clinic. Data were collected 1 year before and 1 year after transfer, using serum creatinine levels, episodes of acute rejection, immunosuppressive therapy, use of steroids, and patient satisfaction as the main outcome measures. Results showed no changes in most clinical outcomes before and after transfer among the three models. However, model 1 was associated with fewer changes in immunosuppressive therapy, and patients in this group reported the greatest satisfaction (100% compared with 64% in model 2 and 78% in model 3).

Finally, as reviewed by the AHRQ, it was found that a less costly "transition coordinator" approach may be an effective way to improve outcomes during transfer for pediatric liver transplant recipients. The transition coordinator role includes preparing patients for self-managed care and transfer before shifting service location and continuing to support patients and both teams afterward. In a prospective study of this approach, patients who used the transition coordinator (n = 20) displayed stable adherence throughout the 2-year study period. Among the 20 enrolled patients, there were no deaths versus 4 of 14 (29%) deaths in a historical control group.

Posttransfer Considerations

In addition to the use of the types of supportive transition procedures described earlier, the literature encourages the continuous evaluation of self-management skills, treatment adherence, and psychosocial functioning in patients who have transferred to adult care. Whenever possible, standardized and validated measures should be used. Given the multifaceted nature of the dialysis treatment regimen, it may be most helpful to take a multimodal approach to assess adherence rather than relying on a single measure. Assessment of treatment adherence may include physiologic (e.g., laboratory tests measuring dietary adherence), behavioral (e.g., appointment attendance), and/or subjective (e.g., patient, parent, and clinician-report) measures. Repeated assessment of these areas of concern will assist in identifying patients who are struggling with transition and help the adult team organize appropriate support. Another consideration is the incorporation of technology-assisted strategies for patient engagement with treatment, such as customized text/email reminders or interactive mobile apps to encourage and monitor treatment adherence. While this type of approach has primarily been studied in adolescent and young adult kidney transplant recipients, there may be an application to the management of dialysis patients as well.

Functional Outcomes

Many patients encounter emotional concerns during the teenage years, including the emergence of psychiatric symptoms. Importantly, declines in mental health are linked to treatment nonadherence. Studies have shown high rates of depression and anxiety symptoms (i.e., up to 50% of patients in some samples) among adolescent dialysis patients. Female adolescents undergoing dialysis treatment may be at especially high risk for experiencing more severe depressive symptoms.

Data also show that adolescent patients may struggle with self-esteem. Some patients report concerns related to differences between themselves and peers, such as physical differences caused by growth delays or scars from medical procedures. Limitations in social functioning related to feelings of being different from peers, extended time spent receiving medical treatment, or other emotional or contextual factors may also be present. Finally, the presence of cognitive delays or learning difficulties, which are common among children with chronic kidney disease, may further complicate this stage in development and, ultimately, the transitional process.

Mental health concerns may continue into young adulthood or even worsen. A recent multicenter study of 417 young adults receiving kidney replacement therapy found that 30% of patients endorsed psychological morbidity. Furthermore, patients on dialysis were more likely to be impacted than those with a transplant. Thus, the importance of frequently assessing mental health while maintaining awareness of related social and cognitive considerations during this time period is emphasized.

Finally, it is important to consider functional outcomes as well. A large study based in the Netherlands compared children with chronic illnesses, including those with ESRD, with healthy norms on a comprehensive measure of developmental milestones (the Course of Life Questionnaire). The ESRD cohort consisted of both transplanted patients and those on dialysis. Findings suggested that adolescents with ESRD lagged behind the normative sample and other

chronic illness groups. Specifically, ESRD patients achieved fewer milestones in the domains of autonomy (e.g., employment, traveling alone), social development, and psychosexual development. Interestingly, though, "risky" behaviors that are often common among young adults were also less likely in the ESRD sample. Although rarely discussed in transitional programming, findings indicate the need to include a developmental lens for functional outcomes in ongoing efforts.

Conclusions

Dialysis patients face a grueling treatment regimen with high rates of nonadherence, particularly during adolescence. Patients may be especially vulnerable to nonadherence as they progress through a transition to adulthood. This involves both shifting to self-managed care and ultimately leaving pediatrics. A multitude of factors contributes to a successful transition, and it is helpful for providers to consider cognitive, mental health, and/or social concerns that may be interfering with self-management skills and/or medical care more broadly. Special attention to treatment adherence, using multimodal assessment, is recommended. Recent work has shown preliminary support for the use of technology-based strategies to engage young adult patients and promote adherence. This research has primarily focused on kidney transplant recipients but may hold promise for transitioning dialysis patients. Overall, research has begun to emerge demonstrating the utility of services to improve the transfer process. Although the literature lacks randomized controlled trials, existing data provide helpful guidance for adult providers in this setting.

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This article reviews interventions for treatment nonadherence in adolescent and young adult kidney transplant recipients.

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This article describes functional outcomes for different types of pediatric patients, including a cohort with end-stage renal disease.

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This commentary provides an overview of the transition process for pediatric renal patients, with corresponding data.

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